

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202811Orig1s000

MEDICAL REVIEW(S)

Memorandum

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

DATE: August 16, 2012
TO: NDA 202811
Linzess (linaclotide)
Ironwood Pharmaceuticals, Inc.

FROM: Victoria Kusiak, M.D.
Deputy Director, Office of Drug Evaluation III

SUBJECT: Approval Action

Linzess (linaclotide), a new molecular entity, is a synthetic 14-amino acid peptide developed for the treatment of irritable bowel syndrome with constipation (IBS-C) and for chronic idiopathic constipation (CIC). It is a guanylate cyclase-C (GC-C) agonist and is structurally related to the guanylin peptide family, which consists of three endogenous peptides (b) (4)

These small cysteine rich peptides bind to and activate guanylate cyclase C (GC-C), a cell surface receptor with intrinsic GC-C activity. Similar to (b) (4) peptides, Linzess stimulates production of cGMP through direct activation of the GC-C receptor. The resulting increase in intracellular cGMP produces changes in cellular function.

Linzess and its active metabolite act locally on the luminal surface of the intestinal epithelium to increase secretion of chloride and bicarbonate ions into the intestinal lumen, mainly through activation of the cystic fibrosis transmembrane conductance regulator resulting in increased fluid secretion and accelerated transit of intestinal contents. When tested in a colorectal distention model in rats, orally administered Linzess produced relief of inflammation and stress induced colorectal hyperalgesia. The Linzess-induced reduction in visceral pain is thought to be mediated by increased extra-cellular cGMP which has been shown to decrease the activity of pain-sensing nerves.

This memorandum documents my concurrence with the Division of Gastroenterology and Inborn Errors Products' (DGIEP's) recommendation to approve Linzess 290 mcg orally once daily for the treatment of IBS-C and Linzess 145 mcg orally once daily for the treatment of CIC.

REGULATORY HISTORY

IND 063290 was submitted by Microbia, Inc. on September 30, 2004 for linaclotide for the treatment of IBS-C and other GI indications including CIC. A meeting was held on October 20, 2005 to discuss Phase 2/3 development for IBS-C and CIC.

On April 9, 2007, agreement was reached on 2 Special Protocol Assessments (SPAs) for non-clinical studies.

The IND was transferred to Ironwood Pharmaceuticals, Inc. on April 14, 2008.

An End of Phase 2 Meeting (EOP2) was held for the CIC indication on May 5, 2008. At that meeting, the non-clinical package was assessed to be adequate for filing. Endpoints and study design for CIC trials were agreed to and a request was made for *in vitro* studies to assess the effect of Linzess on CYP enzymes. DGIEP agreed to consider a partial waiver for pediatric assessments. Additional work was requested on a Patient Reported Outcome assessment (PRO) with regard to endpoint assessment.

An additional EOP2 Meeting was held on August 7, 2008 in regard to the IBS-C indication. At that meeting, *in vitro* studies to determine whether Linzess is a P-gp substrate or a P-gp modulator were requested in addition to the CYP3 enzyme *in vitro* studies. Potential indication language as well as study endpoints were discussed. It was determined that study endpoints had not yet been agreed to for this indication. Study endpoint agreement was reached on February 22, 2010, at which time a proposed pediatric plan was submitted.

A pre-NDA meeting was held on March 22, 2011. At that time it was agreed that 2 efficacy studies in support of the IBS-C indication and 2 efficacy studies in support of the CIC indication would be submitted. Additionally it was agreed that efficacy would be assessed separately for the 2 indications, but that safety would be combined across the indications and evaluated as short term (12 week) and long term (12 month) safety information.

The NDA for Linzess was submitted on August 8, 2011, and received on August 9, 2011. The application was granted a standard review. A major amendment received on April 17, 2012 extended the review clock by three months.

CHEMISTRY, MANUFACTURING and CONTROLS

There are no outstanding CMC issues. The proposed testing and acceptance criteria for both the drug substance and the drug product are considered adequate to assure identity, strength, purity, and quality for all requested dosage strengths of Linzess.

CLINICAL MICROBIOLOGY

There are no clinical microbiology issues for this application.

NONCLINICAL PHARMACOLOGY/TOXICOLOGY

The absorption of Linzess and its active metabolite is extremely limited. The achievement of quantifiable plasma levels of either Linzess or its metabolite (lower limit of quantitation: 0.5-3.0 ng/ml) in animals required oral dose levels at least 500 times the

maximum recommended human dose (MRHD) based on a $\mu\text{g}/\text{kg}$ comparison. Systemic exposure was achieved in the general toxicology studies, reproductive and developmental studies, and the carcinogenicity studies; however, neither Linzess nor its active metabolite was detected in human plasma after administration of the recommended dose levels.

Non-clinical safety studies did not detect any safety issues that would impact the approvability of Linzess.

Oral administration of Linzess was well tolerated in adult rats, mice, and monkeys. In a 13-week oral toxicity study in rats, the no observed adverse effect level (NOAEL) was 50,000 $\mu\text{g}/\text{kg}/\text{day}$. In a 26-week oral toxicity study in mice, the NOAEL was 20,000 $\mu\text{g}/\text{kg}/\text{day}$ and in a 36-week oral toxicity study in monkeys the NOAEL was 5000 $\mu\text{g}/\text{kg}/\text{day}$.

Oral administration of up to 100,000 $\mu\text{g}/\text{kg}/\text{day}$ in rats and 40,000 $\mu\text{g}/\text{kg}/\text{day}$ in rabbits produced no maternal toxicity and no effects on embryo-fetal development. In mice, oral doses $\geq 40,000$ $\mu\text{g}/\text{kg}/\text{day}$ produced severe maternal toxicity including death, reduced fetal weights, effects on fetal morphology, and reduced gravid uterine weight. An oral dose of 5000 $\mu\text{g}/\text{kg}/\text{day}$ did not produce maternal toxicity or any adverse effects on embryo-fetal development in mice. This dose is approximately 1000 times the MRHD based on a $\mu\text{g}/\text{kg}$ comparison.

The most notable non-clinical finding was potent lethality in neonatal/juvenile mice. In a dose ranging study, the minimum lethal doses were 50, 100, and 600 $\mu\text{g}/\text{kg}/\text{day}$ when oral dosing was initiated on *post partum* days 7, 14 and 21 respectively. All deaths occurred within 24 hours after the first daily dose. In a 9-week oral toxicity study in neonatal/juvenile mice with dosing initiated on *post partum* day 7, the minimal lethal dose was 10 $\mu\text{g}/\text{kg}/\text{day}$ in mice less than 9 days of age. 5/40 animals died at this dose; however, no signs of toxicity were observed in mice which survived beyond 9 days *post partum* (i.e., after more than two days of dosing). Thus lethality was found to be highly age dependant. The minimal lethal dose in neonatal mice (10 $\mu\text{g}/\text{kg}/\text{day}$) is approximately 2 times the maximum recommended human dose, based on a $\mu\text{g}/\text{kg}$ comparison. The cause of death in the pups which did not have signs of gavage related injury could not be determined due to lack of clinical signs or macroscopic or microscopic lesions.

The lethality of Linzess in neonatal mice is in marked contrast to the relative absence of toxicity seen in adult mice where doses of up to 20,000 $\mu\text{g}/\text{kg}/\text{day}$ produced no adverse effects. Mortality was observed at doses $\geq 40,000$ $\mu\text{g}/\text{kg}/\text{day}$ in pregnant mice, and at doses $\geq 80,000$ $\mu\text{g}/\text{kg}/\text{day}$ in repeat-dose toxicity studies in adult mice. The totality of the mouse toxicity data indicates that Linzess-induced lethality was highly age dependant. There were no deaths seen in juvenile rabbits when dosing of up to 40,000 $\mu\text{g}/\text{kg}/\text{day}$ was begun on day 14.

The applicant has hypothesized that the increased sensitivity of neonatal/juvenile mice to Linzess may be related to the increased expression of intestinal GC-C receptors in young animals (Al-Majali et al., Lab Animal Sci., 49: 254-259, 1999; Cohen et al., Pediatr Res., 20: 555-560, 1986) or possibly to other factors such as those related to an immature GI system (Walthall et al., Birth Defects Research (Part B), 74: 132-156, 2005; Heller, Arch Dis. Child, 26: 195-204, 1951).

The applicant will be required to conduct, as a Post-Marketing Requirement (PMR), non-clinical study(s) to elucidate the mechanism(s) of Linzess lethality in neonatal/juvenile mice. The proposed study protocols will be submitted for Agency concurrence prior to initiation of studies. In addition, until such time as information from these required non-clinical studies is reviewed in detail, labeling for Linzess will contraindicate its use in children up to six years of age, and a black box warning will be incorporated stating that use of Linzess should be avoided in pediatric patients 6 through 16 years of age due to juvenile animal lethality.

Linzess was negative in the Ames test and *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes and was not carcinogenic in rats or mice.

The label will contain a Pregnancy Category C because maternal and fetal toxicities in mice were noted, albeit at high multiples of the MRHD.

CLINICAL PHARMACOLOGY

Systemic bioavailability of Linzess and its active metabolite was found to be negligible following administration of clinically relevant doses of the drug. Systemic exposures were assessed during Phase 1 single dose and multiple dose PK/PD studies and via sparse sampling in Phase 3 trials following a change in formulation. Validated LC-MS/MS methods were used for the detection of the drug and its metabolite in plasma.

Pharmacokinetics:

Linzess is minimally absorbed following oral administration. Concentrations of the drug and its active metabolite in plasma are below the level of quantitation at clinically relevant doses of 145 or 290 mcg, therefore standard pharmacokinetic parameters such as area under the curve (AUC), maximum concentration (C_{max}), and half life (t_{1/2}) cannot be calculated.

Characteristics of drug absorption (C_{max} and T_{max}) have not been elucidated for Linzess as systemic concentrations are negligible following clinically relevant oral dosing.

Linzess is expected to be minimally distributed to tissues given that plasma concentrations are not measurable following oral administration of clinically relevant doses.

Linzess is metabolized within the GI tract to its principle, active metabolite and both are proteolytically degraded within the lumen to smaller peptides and naturally occurring amino acids.

Active peptide recovery in the stools of fed and fasted subjects following daily administration of Linzess for 7 days averaged 5% (fasted) and 3% (fed) with virtually all as the active metabolite.

In a food effect PK/PD study, concomitant food intake did not result in detectable concentrations of drug or metabolite in plasma. In clinical trials, Linzess was dosed 30 minutes prior to breakfast, on an empty stomach.

Drug Interactions:

No drug-drug interaction studies have been conducted with Linzess because neither Linzess nor its active metabolite is measurable in plasma following oral administration of the clinically recommended dose. Because plasma levels are negligible, no systemic drug-drug interactions are anticipated.

Based upon the results of *in vitro* studies, Linzess does not interact with the cytochrome P450 enzyme system and is neither a substrate nor an inhibitor of the efflux transporter P-glycoprotein, (P-gp).

Thorough QT Study:

Because of the limited bioavailability of Linzess, a thorough QT study was not performed. Triplicate ECGs were obtained on a subset of patients in the Phase 3 CIC and IBS-C trials. There was no effect of QT prolongation observed in these ECGs.

Linzess in Breast Milk:

Although Linzess has negligible systemic bioavailability at clinically relevant human doses, given the findings with regard to neonatal/juvenile mice in non-clinical studies, the potential for the existence of an unlikely transporter mechanism allowing for the appearance and/or concentration of Linzess in breast milk should be evaluated. Therefore, in order to inform the nursing mothers' subsection of the label, a PMR will be issued to conduct an appropriate study to assess concentrations of Linzess and its active metabolite in breast milk. Until such data become available, the label will state that "It is not known whether linaclotide is excreted in human milk. Caution should be exercised when Linzess is administered to nursing women."

Immunogenicity:

Formal testing for immunogenicity was not conducted for Linzess as it is a small peptide for oral administration and has no measurable systemic exposure at clinically relevant

doses; however, it has been determined that the development of anti-Linzess antibodies in patients should be assessed as part of a planned post-marketing clinical trial.

Although Linzess is a small peptide, it contains multiple attributes that make it potentially immunogenic. Linzess is a 14 amino acid peptide that contains three disulfide bonds, which is unusual for a peptide that short. As a result it is likely that Linzess has a more ridged tertiary structure than is typical of a 14 amino acid peptide. While antibodies do develop against linear structures such as peptides, conformational epitopes are better antibody epitopes. Therefore the extensive disulfide bridging in Linzess may render it more immunogenic than many 14 amino acid peptides. Additionally, Linzess is long enough to be a T cell epitope which contributes to its immunogenic potential. T cells are generally requires for maintained adaptive immune responses such as class switched (from IgM to IgG, A or E), affinity matures (selection for mutations that increase antibody affinity for the antigen) memory B cell responses. The ideal T cell epitopes for activation via the HLA class 1 pathway are at least 9 amino acids in length and generally no longer than 12 amino acids.

Loss of clinical efficacy was not observed during clinical trials. Therefore the risk that patients may develop clinically important levels of anti-drug-antibodies that cross-react to endogenous guanylin peptide family members is theoretical. Therefore it is appropriate that the assessment for the potential for the development of anti-Linzess antibodies be carried out postmarketing.

Special Populations:

There is no dose adjustment necessary in the elderly (≥ 65 years of age), the renally impaired or the hepatically impaired as Linzess has minimal systemic bioavailability at clinically relevant doses.

Geriatric, IBS-C: The safety and efficacy of Linzess in the elderly were similar to the safety and efficacy seen in those <65 years of age. There was an approximate 5% increase in the incidence of diarrhea and a 2% increase in flatulence as compared to the younger population. Of 1605 IBS-C patients studied in the placebo-controlled trials, 85 (5%) were at least 65 years of age while 20 (1%) were at least 75 years old.

Geriatric, CIC: The safety and efficacy of Linzess in the elderly were similar to the safety and efficacy in the younger population. Of 1275 CIC patients in the placebo-controlled Phase 3 trials, 155 (12%) were at least 65 years of age while 30 (2%) were at least 75 years old.

EFFICACY

IBS-C: The efficacy of Linzess for the management of IBS-C was established in two double-blind, placebo-controlled, randomized, multicenter studies in adult patients. A total of 800 patients in Trial 1 and 804 patients in Trial 2 received treatment with Linzess 290 mcg or placebo once daily. The mean age of the patients enrolled was 43.9 (range

18-87 years with 5.3% \geq 65 years of age). Of the patients, 90.1% were female, 77.4% were White, 18.8% were Black and 12.0% were Hispanic.

All patients met Rome II criteria for IBS and were required to have a mean abdominal pain score of \geq 3 on a 0-10 point numeric rating scale, $<$ 3 complete spontaneous bowel movements (CSBMs: 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 \leq 5 SBMs per week during a 2 week baseline period. The trial designs were identical through the first 12 weeks and thereafter differed only in that Trial 1 included a 4 week randomized withdrawal period (RW), and Trial 2 continued for 14 additional weeks (total 26 weeks) of double blind treatment.

Efficacy was assessed using responder and change-from-baseline endpoints. Results for endpoints were based on information provided daily by patients. A patient was a responder for either 9/12 or 6/12 weeks. An abdominal pain responder was one who had \geq 30% reduction in mean abdominal pain episodes from baseline in a given week for \geq 9/12 or 6/12 weeks of the treatment period. A CSBM responder was one who had \geq 3 CSBMs and an increase of \geq 1 CSBM from baseline for the 9/12 week responder endpoint and an increase of \geq 1 CSBM in a given week for the 6/12 week endpoint. To be a combined responder, a patient had to meet both the abdominal pain and the CSBM criteria in the same week for 9/12 or 6/12 weeks of the treatment period.

In both trials, the proportion of patients who were responders to Linzess 290 mcg was statistically significantly higher than with placebo.

The results for the 9/12 week endpoint were as follows:

- Combined Responders: 12.1% vs. 5.1 % for Linzess and placebo respectively in Trial 1 (treatment difference, 7.0%; 95% CI: 3.2%-10.9%) and 12.7% vs. 3.0% for Linzess and placebo respectively in Trial 2 (treatment difference 9.7%; 95% CI: 6.1%-13.4%).
- Abdominal Pain Responders: 34.3% vs. 27.1% for Linzess and placebo respectively in Trial 1 (treatment difference 7.2%; 95% CI: 0.9%-13.6%) and 38.9% vs. 19.8% for Linzess and placebo respectively in Trial 2 (treatment difference 19.3%; 95% CI: 13.2%-25.4%).
- CSBM Responders: 19.5% vs. 6.3% for Linzess and placebo respectively in Trial 1 (treatment difference 13.2%; 95% CI: 8.6%-17.7%) and 18.0% vs. 5.0% for Linzess and placebo respectively in Trial 2 (treatment difference 13.0%; 95% CI: 8.7%-17.3%).

The results for the 6/12 week endpoint were as follows:

- Combined Responders: 33.6% vs. 21.0% for Linzess and placebo respectively in Trial 1 (treatment difference 12.6%; 95% CI: 6.5%-8.7%) and 33.7% vs. 13.9% for Linzess and placebo in Trial 2 (treatment difference 19.8%; 95% CI: 14.0%-25.5%).
- Abdominal Pain Responders: 50.1% vs. 37.5% for Linzess and placebo respectively in Trial 1 (treatment difference 12.7%; 95% CI: 5.8%-19.5%) and

- 48.9% vs. 34.5% for Linzess and placebo in Trial 2 (treatment difference 14.4%; 95% CI: 7.6%-21.1%).
- CSBM Responders; 48.6% vs. 29.6% for Linzess and placebo respectively for Trial 1 (treatment difference 19.0%; 95% CI: 12.4%-25.7%) and 47.6% vs. 22.6% for Linzess and placebo in Trial 2 (treatment difference 25.1%; 95% CI: 18.7%-31.4%).

During the 4 week RW period in Trial 1, when Linzess was discontinued bowel symptoms returned toward baseline within the first week with no evidence of rebound worsening compared to baseline; abdominal symptoms also returned toward baseline with no evidence of rebound.

CIC: The efficacy of Linzess for the management of the signs and symptoms of CIC was established in two double-blind, placebo-controlled, randomized, multicenter studies in adult patients. A total of 642 patients in Trial 3 and 630 patients in Trial 4 received treatment with Linzess 145 mcg, Linzess 290 mcg or placebo. The mean age of the patients was 47.8 years (range 18-85 years). 88.9% were female, 76.2% were White, 21.5% were Black and 10.0% were Hispanic.

All patients met modified Rome II criteria for CIC and were excluded if they met criteria for IBS. The trial designs differed only in that Trial 3 had a 4-week RW following the 12 week treatment period.

Efficacy of Linzess was assessed using overall responder and change-from-baseline endpoints. Results for endpoints were based on information provided daily by patients. A CSBM overall responder in the CIC trials was defined as a patient who had ≥ 3 CSBMs and an increase of ≥ 1 CSBM from baseline in a given week for ≥ 9 out of the 12 weeks of the treatment period.

The proportion of patients who were CSBM responders was statistically significantly greater in each of the 2 trials with each dose of Linzess (145 mcg and 290 mcg) compared to placebo. In Trial 3 the results were as follows: Linzess 145mcg: 20.3%; Linzess 290 mcg: 19.4%; placebo 3.3% ($p < 0.0001$ for 145 mcg relative to placebo; $p < 0.005$ for 290 mcg relative to placebo). In Trial 4 the results were as follows: Linzess 145mcg: 15.5%, Linzess 290 mcg: 23%, placebo: 6.0% ($p < 0.0001$ for 145mcg relative to placebo; $p < 0.005$ for 290 mcg relative to placebo).

For CSBM and SBM frequency, each dose of Linzess (145 mcg and 290 mcg) demonstrated a statistically significant separation from placebo that was present in the first week and sustained across the 12 weeks of the treatment period ($p < 0.001$ for each dose versus placebo at all time points). The proportion of patients who met criteria of increasing levels of stool frequency compared to baseline at each week over the 12 weeks of treatment was analyzed. At each level a statistically significant greater proportion of

patients treated with either dose of Linzess met the response criteria compared to placebo patients.

During the 4 week RW period in Trial 3 when Linzess treatment was discontinued, bowel function including CSBMs and SBMs returned toward baseline within the first week of withdrawal with no evidence of rebound worsening.

In CIC patients, the 290 mcg dose of Linzess did not consistently demonstrate greater efficacy over the 145 mcg dose, although both doses were statistically significantly better than placebo at all primary endpoints. Therefore the 145 mcg dose is the only recommended dose for the treatment of CIC.

In the Phase 3 open label, long term trials, 3270 patients with both CIC and IBS-C received 290 mcg of Linzess daily. 32% of patients in these trials required dose reduction to the 145 mcg dose secondary to adverse events (AEs). The majority of these events were diarrhea and other GI AEs.

SAFETY

During clinical trials, approximately 4370 patients received Linzess. Oral doses from 72 mcg to 1010 mcg once daily were evaluated. Approximately 2400 patients were treated for 6 months or longer, 1000 patients for 1 year or longer, and 500 patients for 18 months or longer.

In IBS-C placebo-controlled clinical trials (Trials 1 and 2) 1605 adult patients received either Linzess (807) or placebo (798) once daily for 12-26 weeks. Demographic characteristics were comparable across treatment groups.

The most common adverse reactions that were reported in $\geq 2\%$ of Linzess treated patients and at an incidence greater than placebo were: diarrhea (19.8%:3.0%), abdominal pain (5.1%:3.3%), flatulence (4.3%:1.9%), abdominal distension (2.2%:1.1%), viral gastroenteritis (2.6%:1.4%), and headache (4.1%:3.1%).

Diarrhea was the most commonly reported adverse reaction and is consistent with the pharmacologic action of the drug. 19.8% of Linzess treated patients reported diarrhea in the placebo-controlled trials compared to 3% of placebo-treated patients. Of these, 2% of Linzess-treated patients had severe diarrhea compared to 0.0% placebo-treated patients. The majority of cases of diarrhea started in the first 2 weeks of treatment. Defecation urgency, fecal incontinence and dehydration were reported in $\leq 1\%$ of Linzess-treated patients.

5.3% of patients treated with Linzess as compared to 0.4% of patients treated with placebo discontinued treatment prematurely for the following adverse reactions: diarrhea (5.3%; 0.4%), abdominal pain (1.2%; 0.0%).

In CIC: In CIC placebo-controlled clinical trials, approximately 1276 patients were evaluated. Of these, 430 received Linzess 145 mcg, 422 received 290 mcg and 423 received placebo. Demographics between the groups were comparable.

The adverse reactions that were reported in $\geq 2\%$ of Linzess-treated patients and at an incidence greater than placebo in the Linzess 145 mcg and Linzess 290 mcg groups respectively are as follows: diarrhea (16.0% and 14.2% vs. 4.7% for placebo); flatulence (5.6% and 5.0% vs. 5.2% for placebo); abdominal pain (4.0% and 4.7% vs. 3.1% placebo); nausea (3.5% and 4.3% vs. 3.5% for placebo); abdominal distension (3.5% and 3.6% vs. 2.4% for placebo); upper abdominal pain (3.0% and 1.2% vs. 1.7% for placebo); upper respiratory tract infection (5.1% and 3.1% vs. 4.0% for placebo); and sinusitis (3.0% and 2.6% vs. 1.9% for placebo).

Diarrhea was the most common adverse reaction reported with use of Linzess, consistent with its pharmacologic action. In the pooled pivotal placebo controlled trials for CIC, 16% of patients treated with Linzess reported diarrhea compared to 5% of patients treated with placebo. Of these, 2% of the Linzess-treated patients reported severe diarrhea as compared to $<1\%$ of placebo-treated patients. The majority of reported cases of diarrhea started within the first 2 weeks of treatment. Defecation urgency, fecal incontinence, and dehydration were each reported in $\leq 1\%$ of patients treated with Linzess.

In the placebo-controlled trials in patients with CIC, 7.6% of Linzess treated patients and 4.3% of placebo treated patients discontinued prematurely due to adverse reactions. The most common reasons for discontinuation due to adverse reactions in the Linzess-treated groups were diarrhea (4.2%), and abdominal pain (1.1%) as compared to 0.5% (for diarrhea) and 0.7% (for abdominal pain) in placebo-treated patients.

Long term safety: In Phase 3 open label long term safety trials enrolling both IBS-C and CIC patients, the most frequently reported adverse reactions were GI events with 30.4% of IBS-C and 31.4% of CIC patients reporting diarrhea. Other adverse reactions in long term trials were: abdominal pain, 5.1%; urinary tract infection, 4.8%; sinusitis, 4.7%; nausea, 4.6% and flatulence, 3.6%.

In the Linzess clinical development program, 7 deaths were reported. One patient died in the screening period and never received treatment and 2 additional patients died more than 30 days after receiving drug. Two patients died in Phase 3 trials, one of pancreatic carcinoma and another from Fentanyl toxicity. Four patients died in the long term trials, one from esophageal squamous cell carcinoma, one from multiple trauma, and two from morphine toxicity. None of the deaths were judged to be drug related.

Diarrhea, as expected from the mechanism of action of Linzess, was the most frequently reported adverse reaction and as such was specifically evaluated in terms of incidence and severity. Because diarrhea can be associated with symptoms of dehydration such as orthostatic hypotension and dizziness, these events were also specifically evaluated with regard to association with diarrhea. Overall, there were no clinically relevant differences in the incidence or severity of diarrhea adverse events between the IBS-C and CIC groups

and no difference in the discontinuation rates. Dehydration occurred in less than 0.5% of all patients treated with Linzess during Phase 3 trials, and when it occurred, it occurred primarily in patients with diarrhea and in less than 4% of patients with diarrhea. Dizziness occurred in less than 1.5% of patients treated with either placebo or Linzess and was not associated with diarrhea in that most patients reporting dizziness did not have diarrhea. Fewer than 4% of patients with diarrhea experienced dizziness. Orthostatic hypotension occurred very infrequently (3 cases) and when it occurred, it was associated with alternative explanations such as vomiting and reduced fluid intake.

Overall, the safety information available for Linzess is adequate and indicates that Linzess is safe and well tolerated in the adult IBS-C and CIC populations when given at daily doses of 145 or 290 mcg.

ADVISORY COMMITTEE

This application was not referred to an advisory committee because the clinical study design was acceptable, the application did not raise significant safety or efficacy issues, the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment or prevention of disease, and outside expertise was not necessary.

PEDIATRIC CONSIDERATIONS

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

Because studies with Linzess would be either impossible or highly impractical to conduct in very young children with CIC and because it is unclear that Linzess would confer a therapeutic benefit in the birth to 6 months age group, a waiver is granted for CIC patients for ages from birth to 6 months.

Because IBS-C is not well defined in very young patients and there are too few patients to study, a waiver is granted for IBS-C patients for ages from birth to 6 years.

Studies in CIC pediatric patients older than 6 months and in pediatric patients with IBS-C older than 5 years 11 months are deferred at this time until mechanistic studies to determine the cause of the lethality seen in neonatal/juvenile mice can be conducted.

The product label will indicate that Linzess has not been studied and found to be safe and effective for use in pediatric patients. Use of Linzess will be contraindicated in children < 6 years of age, secondary to the lethality seen in neonatal/juvenile mice and the

possibility that this finding may be associated with an immature GI system and an undeveloped blood brain barrier. The age range of contraindication provides a significant safety margin (approximately 10X) with regard to the age of the mice in which lethality was observed and estimated corresponding human age.

In addition to the contraindication, until such time as the study results from the PMR with regard to understanding the mechanism of lethality in neonatal mice can be reviewed, a black box warning will state that use of Linzess should be avoided in pediatric patients 6 through 17 years of age. This information will also appear in the Warning and Precautions section of the label and in the Pediatric Use section.

POST MARKETING REQUIREMENTS AND COMMITMENTS

PREA Requirements:

The above mentioned deferred pediatric studies required by section 505B(a) of the Federal Food, Drug Cosmetic Act are required postmarketing studies and are listed below:

A safety and efficacy study in pediatric patients with IBS-C ages 7 years up to 17 years.

Final Protocol Submission: April 30, 2015
Study Completion: December 31, 2022
Final Study Report Submission: December 31, 2023

A safety and efficacy study in pediatric patients with CIC ages 7 months up to 17 years

Final Protocol Submission: April 30, 2015
Study Completion: December 31, 2022
Final Study Report Submission: December 31, 2023

FDAAA Requirements:

Section 505(o)(3) Of the Federal Food, Drug and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by statute.

FDA has determined that an analysis of postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of serious risk of age related lethality seen in neonatal/juvenile mouse studies. Although pharmacokinetic data suggest that there is little if any systemic absorption of Linzess, a study to assess the potential serious risk posed by the appearance of Linzess in breast

milk is necessary to evaluate the presence or absence of Linzess in breast milk and to inform the label.

Additionally, an analysis of spontaneous postmarketing adverse events reported under subsection 505 (k)(1) of the FDCA will not be sufficient to assess known serious risks of allergic and immune-mediated reactions or to identify unexpected serious risks related to the development of anti-drug antibodies that may cross react with endogenous guanylin peptide family members and lead to deficiency syndromes.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that the Sponsor should conduct the following postmarketing studies:

A nonclinical study in neonatal and juvenile mice to determine the mechanism of death in neonatal and juvenile mice treated with Linzess.

Final Protocol Submission: January 30, 2013
Study Completion: October 30, 2013
Final Study Report Submission: April 30, 2014

A multiple dose milk- only lactation study to assess concentrations of Linzess and its active metabolite in the milk of healthy, lactating but non-nursing female volunteers, using a validated assay in order to appropriately inform the nursing mothers' subsection of the label.

Final Protocol Submission: March 13, 2013
Trial Completion: September 2014
Final Report Submission: September 2015

A study to develop a validated, sensitive, and accurate assay for the detection of anti-Linzess antibodies, including IgM, IgG, and IgA, that are expected to 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 the parameters not assessed in the validation exercise, and the assay SOP will be provided to FDA.

Subsequent to the development of a satisfactory, sensitive assay, a clinical trial to assess development of an anti -drug antibody (ADA) response in patient plasma samples. Validated assays capable of sensitively detecting ADA responses that are expected to be present at the time of patient sampling will be used. Immunogenicity rates and individual patient titers will be evaluated. Adverse events will be collected.

TRADENAME

The Division of Medication Error Prevention and Analysis (DMEPA) has concluded that the proposed proprietary name, Linzess, is acceptable. It was granted on November 11, 2011.

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

/s/

VICTORIA KUSIAK
08/24/2012

CLINICAL REVIEW

Application Type	NDA
Application Number	202-811
Priority or Standard	Standard
Submit Date	August 8, 2011
Received Date	August 9, 2011
PDUFA Goal Date	June 09, 2012
	Extended to September 9, 2012
Division / Office	Division of Gastroenterology and Inborn Errors of Metabolism
Reviewer Names	Primary: Erica L. Wynn M.D., M.P.H. Secondary: Robert Fiorentino, M.D., M.P.H.
Review Completion Date	July 17, 2012
Established Name	Linacotide
(Proposed) Trade Name	Linzess
Therapeutic Class	Laxative (Locally acting Guanylate cyclase C receptor agonist)
Applicant	Ironwood Pharmaceuticals, Inc.
Form	Capsules
Dosing Regimen	145 and 290 mcg
Proposed Indications	1) Treatment of irritable bowel syndrome with constipation 2) Treatment of chronic constipation
Intended Populations	Patients with either chronic idiopathic constipation or IBS-C

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

(b) (4)
It is recommended that Linaclotide 145µg be approved for use in adult patients with chronic idiopathic constipation. Chronic constipation may have a number of underlying etiologies including drugs, gastroparesis, or biochemical or underlying anatomical defects. The applicant enrolled patients into the pivotal trials using modified Rome II criteria for functional constipation, which by definition has no known underlying etiology. Therefore it is recommended that the proposed indication be (b) (4) treatment of the signs and symptoms of chronic idiopathic constipation.

(Note: During the course of product development, the analytical method for determining the potency of the Linaclotide changed. Therefore, the dose strengths of 150µg and 300µg originally used in the protocols are analogous to the 133µg and 266µg used in the clinical study reports for the submitted trials and the final 145µg and 290µg doses proposed by the applicant for the commercial product. Throughout this document, the reviewer makes reference to the Linaclotide 145µg and 290µg doses. Additionally, when necessary, Linaclotide is also referred to by the abbreviation LIN or the proposed tradename LINZESS.)

(b) (4)
Results of the individual pivotal Phase 3 double-blind placebo controlled trials demonstrated that Linaclotide 290µg may not consistently offer additional numeric (or clinically meaningful) treatment benefit over placebo than that observed with the Linaclotide 145µg dose. Furthermore, in the pooled analysis of the two pivotal trials, the treatment differences were 12.0% and 11.5%, for Linaclotide 145µg and 290µg doses, respectively. (b) (4)

(b) (4) Patients with 0 CSBMs/week at baseline would only have an additional 0.5 to 0.6 CSBM/week using the 290µg Linaclotide dose. The clinical meaningfulness of this fractional change has not been established. (b) (4)

In this application, secondary variables were used to assess “patient rating of change questions”. There were 7 key 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 severity of straining
- Change from baseline in 12-week abdominal discomfort
- Change from baseline in 12-week bloating
- Change from baseline in 12-week constipation severity.

The symptom assessments were very subjective and in the opinion of this reviewer difficult to interpret. It is not clear if the numerical differences observed for the secondary endpoints would also be clinically meaningful. Additionally, patients were asked to reflect on the state of their condition prior to initiation of the trial. With each progressive week, the level of recall bias may have increased, further making these results less useful for interpretation. The p values for all key secondary efficacy parameters were statistically significant using the applicant’s prespecified method of statistical analysis and controlling for multiplicity. However, the Division did not previously agree what change in each of parameters would be clinically meaningful. Additionally, the statistical reviewer has questioned the validity of use of the Hochberg technique to control for multiplicity.

The secondary endpoint of “Change from baseline in 12- week CSBM frequency rate” supports the overall responder analysis. This endpoint, along with the “Change from baseline in 12-week SBM frequency rate,” have been included in the labeling of previously approved products for this indication. The results of the clinical trials for Linaclotide show that for both CSBM and SBM frequency rates, treatment resulted in a change that was greater than 1/week over baseline when compared to placebo. Included within the definition of “Overall Responder” is a requirement that patients have at least an increase of 1 CSBM/week in order to represent a clinically meaningful response. Therefore it would be difficult to justify excluding CSBM and SBM responder frequencies from the labeling based on the changes observed in the trial. The CSBM and SBM frequency rate are objective measures which may be included in the labeling. (b) (4)

The reader is referred to Section 6.1.5 of this review and to the review of the biostatistician for more information.

The applicant has not requested any indication in pediatric patients. However the applicant has submitted a pediatric plan which was presented to the PeRC Committee on May 9, 2012. For the chronic constipation indication, it is recommended that PREA-required trials be waived for pediatric patients under the age of 6 months and deferred for pediatric patients ≥ 6 months to 16 years, 11 months. This is consistent with Divisional policy for other products approved for use in this indication. Given the lethality that occurred during the nonclinical trials in juvenile mice, clinical trials in all pediatric age groups should not commence until the results of additional nonclinical trials are reviewed. To prevent off-label use in pediatric patients, it is recommended that this product be contraindicated in pediatric patients at least up to age 6 years. The labeling should include additional language in the Warning and

Precautions Section to avoid use in all pediatric patients until the mechanism of lethality in the nonclinical trials is better understood. A boxed warning and medication guide may also be justified for this product.

1.2 Risk Benefit Assessment

Adults

Chronic Idiopathic constipation, also known as functional constipation, is estimated to affect between 2 and 28% of Americans.¹⁰ The wide range of prevalence data reflect differences in definitions of the disease. Patients with chronic idiopathic constipation (i.e., constipation not caused by a specific underlying disease, structural, or biochemical anomaly) can be divided into two main categories: those with difficulty defecating (but with normal bowel motion frequency) and those with a bowel transit abnormality (which can present as infrequent defecation).⁸ There are a wide range of perceived “normal” bowel habits, as well as a diverse array of signs and symptoms associated with constipation. The National Digestive Diseases Information Clearing House of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) states that functional constipation is often the result of poor dietary habits and lifestyle and usually implies that the bowel is healthy but not functioning properly. In this context, functional constipation is considered a symptom and not a disease in and of itself.

Risk factors for chronic idiopathic constipation include female sex, older age, inactivity, low caloric intake, low-fiber diet, low income, low educational level, and taking a large number of medications. Although chronic idiopathic constipation is not life-threatening, for those who experience constipation that is refractory to treatment, the condition can be serious and lead to complications such as hemorrhoids and anal fissures. Chronic idiopathic constipation, if severe, may also lead to severe or chronic rectal prolapse which may require surgery. Prolonged chronic idiopathic constipation may also result in fecal impaction and megacolon. This is particularly common among older patients, pregnant women, and those with colonic inertia. Some patients with chronic idiopathic constipation require total abdominal colectomy with ileorectal anastomosis to relieve symptoms

There are few prescription therapies available for the treatment of chronic idiopathic constipation. Lubiprostone (Amitiza®) is indicated for chronic idiopathic constipation.. Tegaserod (Zelnorm®) was approved for chronic constipation, however, it was withdrawn in March 2007 due to cardiac safety concerns and is now available only for emergency use under treatment INDs. None of the prescription drugs have been proven to be safe and effective in pediatric patients. Of the available over-the-counter products, none are designed to be used chronically. There is the also concern for the potential misuse (abuse) of taking OTC products at unsafe doses. Therefore, there may be an unmet medical need for prescription therapies for chronic idiopathic constipation, particularly in individuals who have failed other treatment options.

Two double-blind, placebo-controlled phase 3 clinical trials, evaluating the safety and efficacy of Linaclotide 145µg and 290µg doses, used the following responder definition as the primary endpoint:

- Overall Responder = a patient with at least 3 complete spontaneous bowel movements (CSBMs) per week and an improvement of at least 1 CSBM/week over baseline for at least 9 out of 12 weeks.

Patients with chronic idiopathic constipation treated with both doses of Linaclotide had a statistically significant higher response rate for the primary efficacy endpoint compared to placebo. In trial LIN-MD-01, the CSBM overall responder rates were: placebo 5.6%, Linaclotide 145µg 15.5%, and Linaclotide 290µg 20.3%. In trial MCP-103-303, the CSMB overall responder rates were: placebo 3.3%, Linaclotide 145µg 20.3%, and Linaclotide 290µg 19%. The overall responder rates were numerically low but in the range of what would be expected based on previous experience from clinical trials of products developed for the same indication. The effect of Linaclotide appeared to be maintained over the 12 weeks of the treatment period. There are no data on the durability of efficacy beyond 16 weeks. Trials that are at least 12 weeks in duration are acceptable for therapies that are used to treat chronic conditions. Given the comparable treatment effects over placebo observed with the two doses; the numerically discrepant results of the pivotal phase 3 trials as well as analyses of the adverse event profiles for each dose, there does not appear to be any additional benefit offered by the 290µg dose. The 145µg dose appears to be the lowest effective dose.

..

There were 4 deaths that occurred in patients with chronic idiopathic constipation during the clinical development program (2 during the double-blind placebo-controlled trials and 2 during the long-term safety trials.) None of the deaths appear to be related to Linaclotide. The most commonly occurring adverse event in the Linaclotide clinical development program was diarrhea which occurred in 16% of patients treated with Linaclotide 145mcg, 14.2% of those treated with Linaclotide 290µg, and 5% of those treated with placebo. Most cases were mild to moderate in intensity. Diarrhea was also the most common reason for discontinuation from the clinical program and occurred more often in Linaclotide-treated patients than placebo. This is consistent with the pharmacodynamic action of the drug.

Linaclotide does not appear to increase the risk of gallbladder disease over the background rate of what would normally be found in the general population. Although decreases in white blood cell counts were seen in Linaclotide-treated patients, there were no increases in infections or infestations over placebo.

Three cases of ischemic colitis were reported during the clinical development program of Linaclotide for IBS-C and CIC. Additional safety analyses to characterize the risk of Linaclotide-associated ischemic colitis were inconclusive. An association between Linaclotide and ischemic colitis was not obviously apparent based on the information that was provided. The diagnosis of ischemic colitis requires a high index of suspicion. It may not be possible to determine the true risk of ischemic colitis in the premarketing setting, due to how adverse event data are reported and coded in the clinical trials, and because of the underlying difficulty of making a definitive diagnosis of ischemic colitis. Although a causal relationship between this product and ischemic colitis has not been established, given the seriousness of

the condition, the labeling should include additional language for physician and patient education to warn of the signs and symptoms of ischemic colitis and to mitigate the risk of adverse outcomes secondary to unevaluated and untreated ischemic colitis.

Pediatrics

The applicant has not requested labeling nor proposed that this product be used in pediatric patients for any indication at this time. The applicant has requested a waiver to conduct PREA-required pediatric trials in patients less than 6 months of age. The applicant has requested a deferral to conduct PREA-required trials in pediatric patients from 6 months through 16 years of age.

Constipation in pediatric patients is nonlethal, usually functional in nature (that is- without objective evidence of a pathological condition) and the result of voluntary stool retention following painful bowel movements. Chronic constipation is common among pediatric patients in the Western world with an estimated prevalence of about 3%. The applicant has requested a waiver to conduct PREA-required pediatric trials in patients less than 6 months of age. A waiver seems reasonable because the disease does not exist in this age group. Technically, Chronic idiopathic constipation (also referred to as functional constipation) requires a child to be at least 4 years of age before the condition can be diagnosed by Rome criteria.¹ In the youngest pediatric population with constipation, it is important to rule out an organic cause of first.^{2,3} Furthermore, pediatric patients who are breast fed require special consideration as there are differences in the frequency of constipation occurrence among breast-fed infants and formula-fed infants. Consequently, less frequent stooling may not truly be constipation in infants. For those infants that are diagnosed with “functional constipation” there are a number of treatment alternatives and products used off-label. First-line therapy includes family education and dietary modification. If these fail, disimpaction with glycerin suppositories has been used. Additionally, although neither is recommended for use in infants, both mineral oil and lactulose have been used safely and effectively in practice.^{2,3}

The applicant has requested a deferral to conduct PREA-required trials in pediatric patients from 6 months through 16 years of age. Functional constipation in pediatric patients is nonlethal. There are no evidenced-based guidelines for the evaluation and treatment of constipation in children.³ Like adults, there are a number of nonpharmacological therapies and pharmacological therapies used off-label in pediatric patients.^{3,4} The general approach to management of the child with functional constipation is to

- 1) determine if fecal impaction is present and treat if present
- 2) initiate treatment with oral medication following disimpaction
- 3) provide parental education and close follow-up
- 4) adjust medications as necessary.³

Polyethylene glycol electrolyte solution, given in low doses may be effective long-term treatment for constipation that is difficult to manage.³ Mineral oil, magnesium hydroxide, lactulose, senna, bisacodyl and sorbitol are also available. The use of medication in combination with behavioral management can decrease the time to remission in pediatric patients with chronic constipation.³

There are no clinical safety and efficacy data for the use of Linaclotide in any pediatric population. The results of the nonclinical review revealed lethality in juvenile mice equivalent to pediatric patients ages 0 to 23 months. Lethality in juvenile rabbits was not observed, however the deaths in the juvenile mice occurred at a dose that is only 2 fold greater than the highest dose proposed by the applicant for use in adults. The mechanism of action for the deaths is unknown. There are no nonclinical data in juvenile mice to provide any information that corresponds to pediatric patients ages 2 to 12 years. Based on the nonclinical information that was provided in the application, the nonclinical reviewer has concluded that it may be safe to proceed with pediatric trials in adolescent patients ages 13 years and older. Given the development and physiology of the adolescent GI track relative to the adult GI track, this seems reasonable.

There are previous data (although limited) that demonstrate guanylate cyclase activity in the small intestine of humans varies by age with maximal activity in younger patients that decreases over time.⁵ This data also suggests that the number of guanylate cyclase receptors continues to decrease in humans until at least 60 months of age (5 years) in both the colon and small intestine at which time it seems to begin a plateau but continues to decrease.⁶ However, the number of older patients included in these previous trials is small and therefore the investigators stated that the results should be interpreted with caution. Finally, there are previous data showing that the binding capacity (i.e. number of binding sites/receptor density) of small intestinal and colonic ST_a receptors, which are considered to be analogous with the G-CC receptors also varies with age.⁷

The applicant asserts that the deaths seen in the neonatal mice were most likely explained by increase intestinal secretion in a markedly underdeveloped mouse intestinal tract. In other words, deaths in neonatal mice were secondary to an exaggerated PD response. However, there are no definitive data to support this theory nor has the applicant provided the full characterization of the G-CC receptor over time in juvenile mice.

At this time there does not appear to be enough information to fully assess the risks to pediatric subjects. Additional information is required prior to completion of the full benefit:risk assessment for all pediatric populations. However based on the information provided and in consideration of the condition being treated and the number of alternative products, it does not seem prudent to use this product in any capacity in the pediatric patient until additional nonclinical data have been gathered and reviewed. Based on what is presently known, it appears that the risks do not outweigh the benefits for this vulnerable population.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There is no recommendation for a Postmarket Risk Evaluation and Mitigation Strategy. Routine post-marketing surveillance should be performed with particular attention given to ischemic colitis, decreases in white blood cell count (especially lymphocyte count), diarrhea, dehydration, and indicators of orthostatic hypotension.

1.4 Recommendations for Postmarket Requirements and Commitments

It is recommended that additional nonclinical trials be conducted prior to the commencement of trials required under PREA for pediatric patients.

2 Introduction and Regulatory Background

In clinical practice, constipation has been defined by physicians as three or fewer bowel movements per week.⁸ There tends to be a discrepancy between the way that patients define constipation and the way that physicians define constipation.^{8,10} “While most health care providers define constipation based on stool frequency, patients define constipation as a multi-symptom disorder that includes hard stools, straining, pain when passing a bowel movement and a feeling of incomplete evacuation.”¹⁰ There is a wide range of perceived “normal” bowel habits, as well as a diverse array of signs and symptoms associated with constipation.¹⁰ The Rome criteria provide a definition of constipation based on objective (e.g. stool frequency) and subjective symptoms. At present, Rome III Diagnostic Criteria for functional constipation are :

- Must include 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 3 defecations per week
- Loose stools are rarely present without the use of laxatives
- Insufficient criteria for irritable bowel syndrome

Criteria must be fulfilled for the past three months with symptoms onset at least 6 months prior to diagnosis.⁹

The applicant provided literature which stated that the prevalence of chronic constipation is between 12% and 19%. In other literature references, the prevalence of constipation in the worldwide general population is estimated to range from 0.7% to 79% with a median value of 16%.¹⁰ Estimates of the prevalence of constipation range from 2% to 28% of Americans.^{11,12} The discrepancies that exist in reporting the incidence and prevalence of constipation may be secondary to discrepancies in the definition used.

Chronic constipation may be primary (idiopathic) or due to secondary causes. Risk factors for constipation include female sex, older age, inactivity, low caloric intake, low-fiber diet, low income, low educational level, and taking a large number of medications.^{8,10,11}

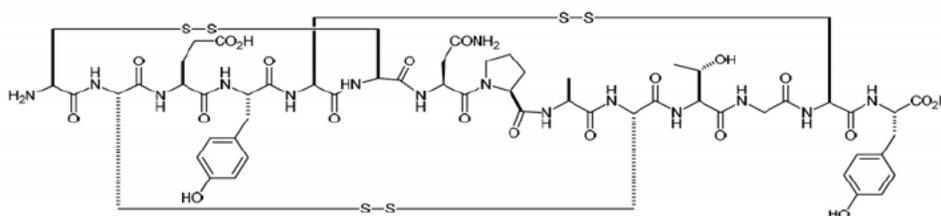
2.1 Product Information

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

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)

Structural Formula:



(b) (4)

Linaclotide is a first-in-class 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, MM419447, 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.

2.2 Currently Available Treatments for Proposed Indications

2.2.1 Prescription Therapies

There are a limited number of approved prescription products for chronic idiopathic constipation. Zelnorm® (tegaserod maleate) tablets were originally approved for women with constipation predominant irritable bowel syndrome (IBS-C) in 2002 and in patients less than 65 years of age with chronic idiopathic constipation in 2004. Subsequently, the drug was withdrawn from the U.S. market due to an association with ischemic cardiovascular events. After removal from the U.S. market in 2007, Zelnorm was later reintroduced and is now available under treatment IND and indicated for the short-term treatment of women with irritable bowel syndrome (IBS) whose primary symptom is constipation. Current labeling states that Zelnorm® is also indicated for the treatment of patients less than 65 years of age with chronic idiopathic constipation. The safety and effectiveness of Zelnorm in men with IBS-C have not been established. Likewise the safety and effectiveness of Zelnorm in patients 65 years or older with chronic idiopathic constipation have not been established. Diarrhea was the most common adverse event in clinical trials of Zelnorm. The labeling also states that serious consequences of diarrhea including hypovolemia, hypotension and syncope have been reported in clinical trials. Cases of intestinal ischemia and ischemic colitis were also reported during the marketed use of Zelnorm.

Amitiza® (lubiprostone) capsules were initially approved in 2006 and are indicated for the treatment of chronic idiopathic constipation in adults and treatment of irritable bowel syndrome with constipation in women ages 18 years and older. The most common adverse events in clinical trials conducted prior to the approval of Amitiza were headache and diarrhea.

According to the current labeling, lactulose is available by prescription for the treatment of constipation. “In patients with a history of chronic constipation, lactulose solution therapy increases the number of bowel movements per day and the number of days on which bowel movements occur.”¹³ Lactulose is a synthetic disaccharide in solution form for oral administration. The drug is poorly absorbed from the gastrointestinal tract and there is no enzyme capable of breaking down the disaccharide present in the human gut. In the colon, lactulose acts as a colonic acidifier, which results in an increase in osmotic pressure and promotes laxation. According to the labeling for lactulose excessive dosage can lead to diarrhea. Common adverse events are flatulence, intestinal cramps, nausea, and vomiting.

2.2.2 Over the Counter Therapies

None of the available over the counter products are designed to be used chronically for constipation. However, a number of as needed treatment options for constipation exist with different mechanisms of action. Fiber supplements and synthetic bulk forming agents are generally considered safe. Bulk forming laxatives are agents of choice as initial therapy for most forms of constipation because they most closely approximate the physiologic mechanism in promoting evacuation. These agents absorb fluid in the GI tract altering

intestinal fluid absorption and electrolyte transport, resulting in expansion of the stool. The resultant increased bulk facilitates peristalsis which increases bowel motility and decreases gastrointestinal transit time. Available bulk forming agents include methylcellulose. Products containing psyllium are no longer generally recognized as safe and effective (GRASE). The FDA decided on this action after reviewing multiple reports of esophageal obstruction associated with the use of granular forms of psyllium laxative. On October 1, 2007, all products that fell under this category were to be discontinued or reformulated to comply with this FDA ruling. This final ruling did not apply to psyllium laxatives in nongranular dosage forms, such as powders, tablets, or wafers.

Hyperosmotic laxatives draw fluid into the bowel from the surrounding tissue and provide for softer stools and increased peristalsis. The hyperosmotic laxatives include nonabsorbable saline products, sorbitol, lactulose, and polymer products. Polyethylene glycol (PEG 3350) has been used for decades. Miralax®, a preparation of polyethylene glycol without electrolytes, was approved for marketing in the U.S. on February 18, 1999. On October 6, 2006, the product became available over-the-counter. Clinical trials have evaluated the safety and efficacy of polyethylene glycol in doses of 17g/day for up to 6 months. Abdominal pain, abdominal bloating, abdominal cramping, flatulence and nausea/vomiting were reported during these trials. Higher doses also produced diarrhea and fecal incontinence. Oral magnesium sulfate preparations are included in the class of saline laxatives and include such products as Almora, Mag-G, Mag-200, Maginex, Magonate liquid. The most frequently reported adverse reaction with oral magnesium salts is diarrhea. Lactulose is a synthetic product that can not be hydrolyzed by any gastrointestinal enzyme resulting in oral doses reaching the colon virtually unchanged. The normal bacterial flora of the colon degrades lactulose into lactic acid and small amounts of formic and acetic acid. This intracolonic breakdown of lactulose increases osmotic pressure resulting in fluid accumulation and increased peristalsis. At the initiation of therapy, patients may experience gaseous distension with flatulence, eructation, abdominal discomfort or crampy pain. Diarrhea may also occur with excessive dosing.

Stimulant laxatives include bisacodyl (available brand names Dulcolax®, Correctol®) senna (Black-Draught®, Agoral®, Ex-Lax®, Senokot®), cascara and dehydrocholic acid. Stimulant laxatives work by direct stimulation of the smooth muscle of the colon. Concerns over the potential carcinogenicity of stimulant laxatives prompted the FDA to review the status of stimulant laxatives. Studies suggested that phenolphthalein, an ingredient in some stimulant laxatives, might increase a person's risk for cancer. The active ingredient in senna appears to be glycosides of danthron, a compound that was withdrawn due to concerns for tumorigenicity. In 1998, the FDA proposed to amend the final monograph for OTC laxative products to reclassify certain stimulant laxative ingredients, including aloe, bisacodyl, casanthranol, cascara sagrada, and senna, from Category I (generally recognized as safe and effective) to Category III (further testing is required), until more data were available. Many products formerly containing stimulant laxative ingredients like cascara or casanthranol have been reformulated.

Stool softeners such as docusate (tradenames include Colace®, Diolase®, Doculax®, Kaopectate®) encourage bowel movements by helping liquids mix into the stool, preventing

dry, hard, stool masses. Although stool softeners, do not directly result in a bowel movement, they do allow the patient to pass stool without straining. Similarly lubricant laxatives (e.g. mineral oil) when taken by mouth encourage bowel movements by coating the bowel and the stool mass with a waterproof film facilitating the easy passage of stool.

Enemas are also available for the relief of constipation. These products work by mechanical distention of the bowel resulting in evacuation of stool. There are also combination products available over the counter. For example, an over the counter product may contain both a stool softener and a stimulant laxative. In general the combination products are more likely to cause side effects because of the presence of multiple ingredients.

2.2.3 Behavioral Therapies

Lifestyle modifications (such as increased exercise, increased fluid intake and increased dietary fiber) are options for improving the symptoms of constipation. The LIFELAX trial conducted in the United Kingdom attempted to investigate the effectiveness of laxatives versus dietary modifications. However, low enrollment precluded the authors from drawing any firm conclusions. To date there is insufficient evidence supporting the effects of nondrug interventions, although some studies have shown them to be potentially beneficial.

2.3 Availability of Proposed Active Ingredient in the United States

The product of this NDA is a new molecular entity and not available on the market in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

The product of this NDA is first in class. Prescription products being developed for IBS-C and chronic idiopathic constipation have been associated with severe diarrhea resulting in dehydration and electrolyte abnormalities along with their associated sequelae. Products being developed for these indications have also been plagued by concerns of the development of intestinal ischemia in patients taking the medications. The most frequent form of mesenteric ischemia is ischemic colitis, which tends to occur in older patients. Etiologies of the condition may include hypotension (resulting in inadequate intestinal blood flow or emboli), thrombi, or vasoconstriction of the mesenteric arteries.¹⁴ Increased intracolonic pressure due to impacted feces or enema injury has also been linked to colonic ischemia. Ischemic colitis may manifest itself as a rapid onset of abdominal pain, bloody diarrhea, or rectal bleeding.^{14,15} Most cases of bowel ischemia are transient, nongrangerous, and resolve without sequelae.¹⁵ However, some cases are more severe. The transient nature of the condition contribute to the difficulty in estimating the incidence of ischemic colitis, as most cases are either not reported or misdiagnosed.¹⁵ (See section 7.7.1 for more information)

2.5 Summary of Presubmission Regulatory Activity Related to Submission

For additional details on the presubmission regulatory activity, the reader is referred to Appendix 9.5

August 4, 2004	Type B meeting to discuss the use of MD-1100 acetate for the treatment of constipation predominant irritable bowel syndrome (IBS-C), (b) (4) and chronic idiopathic constipation (CC). In lieu of a face to face meeting, the sponsor accepted written responses sent on July 14, 2004.
September 30, 2004	IND 63290 was submitted by Microbia, Inc. for a Phase 1 study to be conducted with MD-1100 Acetate for the treatment of IBS C. Study is deemed safe to proceed. Doses studied were 30µg, 100µg, 300µg, 1000µg, and 3000µg among 5 separate cohorts.
November 9, 2004	Advice letter to sponsor—Obtain 12 lead ECG at 24 and 48 hours post dose to fully evaluate any potential drug-associated ECG effects. Conduct a quantitative fecal and urinary recovery of the drug and metabolites in a mass balance study.
May 5, 2005	Teleconference with sponsor to discuss amendments to Protocol MCP-103-002 entitled “Clinical Protocol for a Seven Day, Oral Multiple Ascending Dose, Placebo-Controlled Study of MD-1100 in Healthy Subjects”.
October 20, 2005	Type C Industry Meeting with Sponsor
February 13, 2006	Advice letter sent to sponsor related to the Chronic Idiopathic Constipation Indication.
June 5, 2006	Teleconference between Microbia and the Division of Gastroenterology Products. Sponsor to discuss endpoints for Chronic Idiopathic Constipation
June 12, 2006	Advice letter providing detailed instructions related to toxicology study requirements.
September 25, 2006	Meeting with Sponsor to discuss primary and secondary endpoints for IBS-C clinical trials as well as the overall clinical development program.
January 11, 2007	Meeting between the Sponsor and the Agency to discuss the necessity for human and animal mass balance studies, carcinogenicity studies, and the use of an absolute dose for the planned chronic toxicology studies.
February 15, 2007	Advice letter to sponsor from nonclinical. Additional nonclinical study reports are needed for review prior to the initiation of the Phase 3 trials.
February 22, 2007	Advice letter to sponsor regarding nonclinical issues.
April 6, 2007	SEALD review states that primary endpoint for clinical trials is not acceptable and recommends revisions.
April 9, 2007	Sponsor requests SPA agreement for nonclinical carcinogenicity studies.
April 19, 2007	Type B Meeting between the sponsor and Agency to discuss primary endpoint used in IBS-C phase 2b and 3 clinical trials, duration of treatment and administrative issues.
April 14, 2008	Sponsorship of IND 63,290 changed from Microbia to Ironwood Pharmaceuticals
May 7, 2008	SEALD review of primary endpoint for Chronic idiopathic constipation trials. The primary efficacy endpoint will be complete spontaneous bowel movement overall responders for 9 out of the 12 weeks of the trial.
May 15, 2008	End of Phase 2 meeting held. Sponsor seeking agreement concerning the Phase 3 trials, the impact of the renal clearance rate data, and pediatric deferral. Separate End of Phase 2 meeting held for IBS-C indication.

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August 7, 2008	Type B End of Phase 2 meeting to discuss the Phase 2 program for IBS-C.
September 3, 2008	Advice Letter to the sponsor stating that a TQT study is not needed for Linaclotide..
October 14, 2008	Type A meeting. Additional discussions between Agency and Sponsor regarding the IBS-C endpoints.
November 6, 2008 -	End of Phase 2 Chemistry Manufacturing and Controls (CMC) meeting held. (Meeting minutes revised June 01, 2009)
April 4, 2009	Nonclinical Advice letter.
November 17, 2008	Letter Correspondence between Agency and Sponsor
January 26, 2010	IND 63,290 Type C meeting to discuss the adequacy of the proposed pediatric plan for Linaclotide. [Pediatric Maternal Health Staff and Patient-Reported Outcome (PRO) Team consulted] Pediatric dosing trials may not commence until after the NDA review of safety
May 20, 2010	CMC meeting to discuss the development of Linaclotide
May 20, 2010	Advice letter to the sponsor stating that at least 4 complete IVRS calls per week are necessary for inclusion in the weekly responder analysis, otherwise patients will be considered nonresponders. Agency recommends that sponsor retains the original prespecified definition of a weekly CSBM responder. If the definition is changed prior to database lock, than the clinical meaningfulness will be a review issue. If the definition of an overall responder is changed, than sponsor should analyze data using both the original overall responder definition and the revised definition.
January 20, 2011-	IND 63,290 Type C meeting to reach agreement on CMC development program. In lieu of quantifying peptide content applicant proposed to quantify Linaclotide content. The sponsor will provide detailed information about the conversion factor used to arrive at the commercial dose when the NDA is submitted.
March 22, 2011	Type B Pre-NDA Meeting
May 11, 2011	Pre-NDA CMC Meeting scheduled for this time was cancelled. Sponsor accepted preliminary comments dated May 4, 2011. Sponsor encouraged to continue to collect data to determine if the routine manufacturing and testing programs produce consistently acceptable product lots. Manufacturers overall stability plan is acceptable. The planned structure and organization of the quality sections are acceptable

2.6 Other Relevant Background Information

The section is not applicable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of reasonable quality to begin the review. At the time of this review completion, there were 36 solicited information requests to clarify information in the application. There was some splitting of the adverse events terms in the datasets. For example, the applicant's decode contained the terms abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness and abdominal discomfort. It is not clear how the distinction in the coding of verbatim terms to these decoded terms were made. "Black stools" and "dark stools" were coded as "faeces discolored" yet "black tarry stools" was coded as "melaena". Likewise, "abdominal spasms" were coded to "abdominal rigidity" yet "abdominal cramping" was coded to "abdominal pain" while "stomach cramps" and "stomach cramping" were coded to "upper abdominal pain." Another example would be the splitting of terms for "diarrhea" vs. "frequent bowel movements" and "gastrointestinal motility disorder" vs. "ileus".

According to the applicant, a review of patient data listings for all the double-blind, placebo-controlled Phase 2 and Phase 3 trials, was completed after the databases were locked and the studies unblinded. This review revealed that a number of patients shared similar demographic profiles (e.g., date of birth, initials, gender, and geographic region). Further investigation of source documents at study sites confirmed that in the Phase 3 clinical program, there were 25 cases of patients who enrolled more than once, either in the same trial or in multiple Phase 2 and 3 trials in violation of entry criteria. Throughout the summaries, these cases were referred to as "duplicate patients." One patient (#0240105) enrolled in and completed Trial LIN-MD-01 and later enrolled in and completed Trial MCP-103-303 as patient #01230004. This patient was not excluded from the psychometric analysis.

Please refer to the clinical inspection summaries of Dr. Roy Blay. In addition to an inspection of the IND sponsor, Forest Laboratories, Inc., inspections by the Office of Scientific Investigation of the following sites were conducted:

- Site 5 for Protocol MCP-103-303 due to high enrollment and efficacy results
- Site 10 for Protocol MCP-103-303 due to high enrollment and efficacy results
- Site 61 for Protocol LIN-MD-01 due to high enrollment, significant efficacy results and an increased average number of adverse events
- Site 95 for Protocol LIN-MD-01 due to high enrollment and efficacy results
- Site 8 for Protocol LIN-MD-01: a foreign site.

The inspector concluded that data submitted by the sponsor appeared to be adequate to support the proposed indications. Three sites were issued a form FDA 483 after inspections revealed regulatory violations. The inspector concluded that the protocol deviations observed at these sites did not appear to have a substantial effect on the final safety and efficacy evaluations.

3.2 Compliance with Good Clinical Practices

Within each of the clinical study reports, the applicant submitted statements that the trials were conducted in compliance with ICH-E6 Good Clinical Practice.

3.3 Financial Disclosures

All clinical trials and studies for this application were conducted by the applicant, Ironwood Pharmaceuticals, Inc. and the applicant's partner, Forest Laboratories, Inc. As required in 21 CFR 54.4(a)(1), financial disclosure forms were collected from investigators participating in each of the studies submitted in support of the application. According to the applicant, disclosure forms were collected from each of the study sponsor's partners also. However, Ironwood was a privately held entity at the initiation of the Phase 3 trials. Therefore, for studies conducted by the applicant's partner, disclosure forms regarding financial interests and arrangements between the investigator and Ironwood were not collected until after Ironwood's initial public offering and were not available for all investigators.

The following table reproduced from the Applicant's submission provides a summary of study sponsorship.

Table 1 Table Summarizing Trial Sponsorship

Study Number	Study Sponsor	Scope of Financial Disclosure Information	Note
MCP-103-201*	Ironwood (formerly Microbia)	Ironwood	* These two Ironwood-sponsored studies were completed prior to the formation of the Ironwood and Forest partnership, therefore disclosure forms regarding financial interests and arrangements between clinical investigators and Forrest were not collected.
MCP-103-202*	Ironwood (formerly Microbia)	Ironwood	
MCP-103-302	Ironwood	Ironwood and Forest	
MCP-103-303	Ironwood	Ironwood and Forest	
LIN-MD-01#	Forest	Ironwood and Forest	# For these two Forest-sponsored studies, disclosure forms regarding financial interests and arrangements between clinical investigators and Ironwood were collected after Ironwood's initial public offering (February 02, 2010), which occurred after study initiation.
LIN-MD-31#	Forest	Ironwood and Forest	

According to the applicant, none of the clinical investigators or subinvestigators, directly involved in the treatment or evaluation of research participants was a full-time or part-time employee of either of the study sponsors.

For those clinical investigators and sub-investigators for whom the study sponsor was unable to obtain the necessary information required for financial disclosure/certification, the applicant provided a statement certifying that the sponsor acted with due diligence in attempting to obtain the information. Trial MCP-103-202 was a phase 2b trial in patients with IBS-C. Trial MCP-103-201 was a 4 week phase 2b dose-ranging trial in CIC patients and trial LIN-MD-01 was a pivotal 12 week phase 3 study submitted in support of the safety and efficacy of Linaclotide for the chronic idiopathic constipation indication. According to the applicant, completed financial disclosure forms could not be obtained from 7 of the subinvestigators in Trial LIN-MD-01. These investigators were from sites 056 and 094. Site 56 enrolled 5 study participants and site 94 enrolled 8 study participants. In the absence of reviewing the financial disclosure forms, the potential for financial bias can not be completely ruled out. However, it is unlikely that these sites could markedly alter the overall efficacy outcome results. Per the statistical reviewer when the sites were omitted from the efficacy analysis, the overall outcome results did not change.

An FDA form 3455 was submitted for investigators who had financial information to disclose. Two investigators received speaker payments for Fibromyalgia and/or Savella programs. The presentations were limited to approved “on-label” use of products approved for a separate medical condition that is not the subject of this NDA. Therefore the potential for bias as a result of these financial relationships is small.

Another principal investigator received payment for providing consulting and writing services in support of Ironwood’s gastroenterology programs. According to the applicant, the consultant services agreements were initiated at least 6 months after the investigator completed his participation in the NDA study trial. Given this information any potential bias affecting the outcome results of Linaclotide clinical development program appears limited. One sub-investigator received speaker payments for Lexapro Educational Programs. This sub-investigator signed a memo attesting that potential bias on her part would be minimized to the best of her ability. Another sub-investigator whose spouse was an employee of Forest signed statements attesting her spouse had no direct contact or affiliation with the research and development of any products at Forest, nor any Linaclotide study teams. In addition the sub-investigator stated that her participation in the Linaclotide studies had been limited to performing physical exams and that neither she nor her spouse has any significant equity interest in Forest.

The applicant asserts that any financial arrangements between the clinical investigator and the study sponsors were minimized by the following study design elements:

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

The applicant’s arguments appear reasonable.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to the complete product quality review by Dr. Jane Chang for additional details. As of April 3, 2012, the CMC reviewer reported that the NDA was not recommended for approval in its present form due to labeling issues and a site recommendation from the Office of Compliance. However, the NDA had provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The applicant requested a categorical exclusion from the preparation of an environmental assessment under 21 CFR25.31 which was found to be acceptable. Subsequent reports from Dr. Chang, stated that the product was approvable.

Linaclotide is a 14 amino-acid peptide containing three disulfide linkages with an average molecular mass of 1526.8 Daltons. The proposed commercial product is comprised of hard gelatin capsules that contain the Linaclotide drug substance coated onto (b) (4) beads along with (b) (4) (hypromellose) and (b) (4) (calcium chloride dehydrate and L-leucine). The capsules are available in 145µg and 290µg strengths. The 145 µg Linaclotide capsules are immediate-release capsules, supplied as a (b) (4) size 3 white to off-white opaque hard gelatin capsule with a gray imprint "FL 145" on the cap. The capsule contains white to off-white beads. The 290 µg Linaclotide capsules are also immediate-release capsules and supplied as a (b) (4) size 2, white to off-white opaque hard gelatin capsule with a gray imprint "FL 290" on the cap. This capsule also contains white to off-white beads.

The drug substance of Linaclotide is a (b) (4). It has shown to be stable under the recommended storage condition of (b) (4).

The two strengths of the capsule product (145µg and 290µg) (b) (4)

During the course of product development, the analytical method for determining the potency of the Linaclotide primary reference standard changed. (b) (4)

According to the sponsor most recently, a gravimetric approach has been adopted for determination of the potency based on Linaclotide content by correcting for peptide and non-peptide related impurities. The changes made to the approach for determination of the potency of the Linaclotide primary reference standard have consequently resulted in adjustments to the drug product potency label claims.

4.1.1 Product Quality Microbiology

Please refer to the review by Dr. Jane Chang for additional information regarding the product quality microbiology. Stability studies were conducted for the drug substance to support the recommended (b) (4)

. Dr. Chang stated in her review that Linaclotide capsules should be kept in the original container with the dessicant to prevent degradation from moisture. According to Dr. Chang, the stability data submitted for each dose of Linaclotide support the proposed expiration dating periods stated below when stored at 25°C (excursions permitted to 15 - 30°C):

- 15 months expiration dating period for 4-count and 30-count bottle configurations for 290 µg strength.
- 15 months expiration dating period for 30-count bottle configuration for 145 µg strength
- 12 months expiration dating period for 4-count bottle configuration for 145 µg strength.

Please refer to the review of Dr. Jane Chang for additional discussions related to drug strength, drug purity, and degradation of the drug product.

4.2 Clinical Microbiology

Other clinical microbiology considerations do not apply because this product is not intended for use as an antimicrobial.

4.3 Nonclinical Pharmacology/Toxicology

Please refer to the nonclinical review of Dr. Yuk-Chow Ng for complete details.

According to the applicant, "Following oral dosing, Linaclotide is minimally absorbed in all studied species (including mice, rats, and monkeys) with a low absolute oral bioavailability in all animal species." The predominant mechanism of clearance of orally administered Linaclotide (and the active metabolite) is through degradation in the intestine. However fecal recovery studies in rats and humans have shown that a small amount of degradation compounds are excreted in the feces. Consequently a small amount of the active peptide has the potential to interact with GC-C receptors throughout the entire GI tract, including the colon. When administered to animals intravenously, the kidney is a major clearance organ. Clearance also occurs through the biliary system.

According to the applicant, in monkeys watery feces were present at all Linaclotide dose levels evaluated (up to 50mg/kg/day). Repeated daily oral dosing of monkeys for up to 39 weeks did not result in any noticeable decrease in the drug's pharmacological effects on stool consistency, but these effects were reversible upon discontinuation of the drug. There were two monkeys (one male in the 10mg/kg/day group and one female in the 50mg/kg/day group) that experienced severe watery diarrhea to the point of dehydration. These animals were euthanized before the end of the studies. Histology samples from the large intestine (colon, cecum, rectum) showed degeneration and necrosis. There were no histopathology changes identified in the other monkeys evaluated. Based on mortality, the NOAEL in

monkeys administered Linaclotide orally for 39 weeks was determined to be 5mg/kg/day (324-fold over the highest Phase 3 adult clinical dose adjusted for body surface area.)

Nonclinical studies in adult mice revealed conflicting data. During the 13 week repeated dose oral toxicity study in mice, mortality and histopathological lesions in the lymphoid system (spleen and thymus), GI tract, kidney, and heart were observed at doses \geq 100mg/kg/day. However during the 26-week repeated dose oral toxicity study in mice, no microscopic changes were observed at similar Linaclotide dose levels. The NOAEL in adult mice was 20mg/kg/day (324 fold over the highest adult Phase 3 clinical dose adjusted for body surface area). This data may indicate that some tolerance occurs in mice with increased exposure. However, this directly conflicts with information from nonclinical studies in monkeys which show that the pharmacological effect does not change with time. The conflicting data may also be species specific. The applicant asserts that immune-related histopathological findings such as those seen in the 13 week mice study and the 39-week monkey study were “only observed in the presence of general debilitation and related to a ‘stress response’ and, therefore, are not considered directly related to Linaclotide administration.” However, additional information would be required before any conclusions are drawn.

The results from *in vitro* bacterial and mammalian cell genetic toxicity studies and *in vivo* carcinogenicity studies indicated that Linaclotide is not mutagenic, clastogenic or carcinogenic. In the 2-year carcinogenicity studies, Linaclotide was not found to be carcinogenic when administered at oral doses of up to 6000 and 3500 μ g/kg/day in mice and rats, respectively. These doses were calculated to be up to 97-fold and 114-fold the highest proposed human commercial dose adjusted for body surface area.

In reproductive and developmental toxicity studies, Linaclotide at oral doses of up to 100 mg/kg (3243-fold the maximum recommended human dose, adjusted for body surface area) had no effect on fertility, reproductive function or prenatal and postnatal development in male and female rats. In embryo-fetal developmental toxicity studies in rats, at oral doses up to 100 mg/kg/day and in rabbits, at oral doses up to 40 mg/kg/day (2595-fold the maximum recommended human dose, adjusted for body surface area), there was no maternal toxicity and no effect on embryo-fetal development. In mice, at oral doses of 5 mg/kg/day (81-fold above the maximum recommended human dose, adjusted for body surface area) there were no effects on embryo-fetal development. At maternally toxic doses of \geq 40 mg/kg in mice (648-fold the maximum recommended human dose adjusted for body surface area), reduced fetal weights, reduced gravid uterine weights, and effects on fetal morphology were observed. It is not known whether Linaclotide is excreted in human milk.

Studies in juvenile animals indicated that Linaclotide tolerability was related to dose as well as age of the animals. Older animals tolerated the higher dose levels better. At the maximum tolerated doses, there were no effects on physical development or neurobehavioral assessments after Linaclotide was administered beginning on post partum Day 9 and continuing for 9 weeks until the animals were mature. The applicant postulated that increased sensitivity of juvenile mice to Linaclotide may be related to the increased

expression of intestinal GC-C receptors in young animals or other factors related to an immature GI system of the mouse.

A dose ranging study was conducted in juvenile mice which demonstrated a finding of lethality in neonatal mice. Neonatal mice were administered 0.1, 10, 50, 100, and 600 µg/kg/day for 5 days. Adverse clinical signs and death occurred within 24 hr after administration of the 50µg/kg/day dose in 7 day old mice; the 100µg/kg/day dose in 14 day old mice, and 600µg/kg/day dose in 21 day old mice. One pooled plasma sample from male mice that received 30µg/kg/day showed quantifiable levels (13.9 ng/mL) of the active metabolite MM-419447 at 2 hours after a single dose (*post partum day 7*). All remaining plasma samples in all dose groups were below the limits of quantitation for Linaclotide(2 ng/mL) and MM-419447 (5 ng/mL). The nonclinical team concluded that there was insufficient information to evaluate the relevance of this finding to human neonates.

The nonclinical NOAELs identified in the chronic toxicity studies (26-week study in mice and 39-week study in monkeys) are > 300-fold higher than the highest proposed commercial dose. The doses evaluated in carcinogenicity studies are approximately 100-fold higher than the highest proposed commercial dose. In the reproductive and developmental toxicity studies, the nonclinical NOAELs identified are more than 80-fold higher than the highest proposed commercial dose. Even after intravenous administration of Linaclotide to maximize systemic exposure, the nonclinical NOAELs identified were greater than 100-fold higher than the highest proposed commercial dose administered orally. The reader is referred to the nonclinical review of Dr. Yuk-Chow Ng for additional nonclinical information.

There are nonclinical data for juvenile mice with ages that correspond to pediatric patients ages 0 to 23 months and 12 to 16 years of age. There are no nonclinical data corresponding to pediatric patients ages 2 years to 11years, 11months. While the nonclinical data may provide some preliminary evidence that very young pediatric patients may be extremely sensitive to the effects of orally administered Linaclotide and that the sensitivity may decrease with age, this data should be interpreted with caution. Furthermore the lack of nonclinical data to cover the entire range of pediatric age groups would preclude any definitive preliminary conclusions regarding the use of this product across the entire spectrum of the pediatric population. Again the reader is referred to the nonclinical review of Dr. Ng.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Linaclotide and its active metabolite bind to and activate the guanylate cyclase C receptor (GC-C) locally on the luminal surface of the intestinal epithelium. According to the applicant, activation of the GC-C receptor results in an increase in concentrations of cyclic guanosine monophosphate (cGMP), both extracellularly and intracellularly. Extracellular cGMP decreases pain-fiber activity and may result 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

In animal models, Linaclotide was shown to increase gastrointestinal secretion and transit time. Traditional pharmacodynamic parameters (e.g. biomarkers) were not measured in humans. The effects of Linaclotide on bowel habits were evaluated as indicators of the pharmacodynamics of Linaclotide. Assessments of stool consistency (using the Bristol Stool Form Scale); severity of straining (using the Ease of Passage Scale or straining scale); stool frequency; and stool weight were assessed before and after treatment. These parameters were evaluated in healthy volunteers in single and multiple-ascending dose, placebo-controlled Phase 1 trials at baseline and 48 hours post-dose. The change from pretreatment weekly stool scores (using the Bristol Stool Form Scale) was also assessed in a food-effect study. Because the form of the feces largely depends on the time spent in the colon, measuring stool consistency using the Bristol Stool Form Scale was asserted to be representative of GI transit time. Please refer to the clinical pharmacology review for additional discussions regarding the validity of this assertion. The reader is also referred to Appendices 9.3 and 9.4.

The PD effect of oral Linaclotide was determined in IBS-C patients after once-daily dosing of placebo, 97 μ g Linaclotide or 966 μ g of Linaclotide for five days. The primary endpoints were gastrointestinal transit times as measured by the ascending colon emptying half-life (AC $t_{1/2}$) value and the colonic geometric center at 24 hours (GC 24) relative to baseline. Stool consistency, straining, stool frequency, time to first bowel movement after drug intake and completeness of evacuation were measured as secondary pharmacodynamic endpoints.

In these studies, Linaclotide resulted in an increase from baseline in Bristol Stool Form Scale indicating softer, looser stools. The studies also demonstrated that patients strained less (as measured by the Ease of Passage scale). There is an increased pharmacodynamic effect when Linaclotide is administered with food. A statistically significant overall treatment effect was seen for ascending colon emptying time and overall colonic transit at 48 hours. Likewise stool frequency increased, straining decreased, and time to first bowel movement decreased. The reader is referred to the clinical pharmacology review for additional details and information.

4.4.3 Pharmacokinetics

Please refer to the clinical pharmacology review for additional details.

Linaclotide is stable when subjected to acid and intestinal proteases including pepsin, trypsin, chymotrypsin, and aminopeptidase under nonreducing conditions. Upon reaching the intestine, Linaclotide is readily metabolized to MM-419447, which is formed by the enzymatic cleavage of the C-terminal tyrosine of Linaclotide. The single active metabolite, MM419447, has the same pharmacological activity as Linaclotide. This metabolite was formed in all species tested.

The degradation pathway of Linaclotide and MM-419447 initiates when the disulfide bonds are reduced in the intestine, resulting in the loss of tertiary structure rendering both peptides pharmacologically inactive. Linaclotide is poorly absorbed across the intestinal epithelium. The absolute oral bioavailability of Linaclotide is very low. Plasma samples were obtained from healthy volunteers up to 48 hours following administration of single, ascending oral doses of Linaclotide. Plasma samples were also obtained on the first and seventh day of repeated once-daily dosing of Linaclotide. There were no measurable concentrations of Linaclotide or the active metabolite in any of the samples. Consequently, standard PK parameters could not be calculated for Linaclotide or MM-419447.

The applicant also analyzed plasma samples collected from studies designed to determine the effect of food on the pharmacodynamics of Linaclotide. Systemic exposures following a supratherapeutic dose (2897 µg) of Linaclotide, and the highest proposed commercial dose (290µg) were assessed. After seven days of once-daily oral administration of 290µg of Linaclotide, neither Linaclotide nor the active metabolite MM-419447 were detected in any of the study participants. When the seven day-dosing regimen was followed by a single 2897 µg dose on the eighth day, Linaclotide concentrations were quantifiable in the plasma from 2 of the 18 study participants but remained below 1 ng/mL in each case. The metabolite was not quantifiable in the plasma of any of the other subjects.

In conclusion the applicant states that there were not enough quantifiable plasma concentrations for the calculation of standard pharmacokinetic (PK) parameters for Linaclotide or MM-419447. The applicant also argues that traditional PK studies on special populations are unlikely to yield interpretable results and the risk of drug-drug interactions or altered clearance in special populations (e.g. renally or hepatically impaired patients) is minimal given the low systemic bioavailability. The applicant stated that a mass balance study in which radio-labeled amino acids have been broken down into naturally occurring amino acids available for absorption and recycling into endogenous peptides and protein was not conducted. The reader is referred to the clinical pharmacology review.

In vitro studies were conducted to assess the potential of Linaclotide and the active metabolite to inhibit transporters in the liver, kidney and intestine. Similar studies were conducted to assess the induction and inhibition potential of the active peptides for drug metabolizing P450 enzymes. Linaclotide does not inhibit the common intestinal enzymes CYP2C9 and CYP3A4. Linaclotide also did not induce or inhibit liver enzymes.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

There were six randomized, double-blind, placebo-controlled Phase 2b trials and Phase 3 trials submitted in support of the effectiveness and safety of Linaclotide for the proposed indications. The Long-term safety trial included patients with both chronic idiopathic constipation (CIC) and constipation predominant irritable bowel syndrome. (IBS-C). A summary of these trials are provided in the table below. In addition there were three Phase 1 trials that evaluated the safety, pharmacodynamics, and pharmacokinetics of Linaclotide in healthy subjects.

Table 2 Table of Trials Submitted in Support of the Chronic idiopathic constipation Indication

Trial Identification Number	Type of Trial	Trial Objective	Trial Design	Trial Treatment Groups	Trial Population of Interest	Number of Enrollees	Treatment Duration
MCP-103-305	Long-term Safety Trial	To evaluate the Long-term safety and treatment satisfaction of multiple doses of Linaclotide	Open-Label Single Arm	290µg Linaclotide (with option of reduction to 145 µg) once daily;	Patients with Chronic idiopathic constipation or IBS-C	1725 (includes rollover patients who completed with a Phase 2b or Phase 3 study)	Up to 78 weeks (18 months)
LIN-MD-02	Long-term Safety Trial	To evaluate the Long-term safety and treatment satisfaction of multiple doses of Linaclotide	Open-Label Single Arm	290µg Linaclotide (with option of reduction to 145 µg); once daily;	Patients with IBS-C or Chronic Idiopathic Constipation	1553 (includes rollover patients who completed a Phase 2b or Phase 3 study)	Up to 78 weeks (18 months)
MCP-103-303	Efficacy and Safety Trial	To evaluate the efficacy and safety of multiple doses of Linaclotide	Phase 3, Randomized, Double-blind, Placebo Controlled Parallel-Group	145µg Linaclotide or 290µg Linaclotide or Placebo Once daily;	Patients with Chronic Idiopathic Constipation	217 -- 145µg Linaclotide 217 -- 290µg Linaclotide 209 Placebo (643 total)	16 weeks total (12 weeks Double Blind Treatment Period + 4 weeks Randomized Withdrawal)
LIN-MD-01	Efficacy and Safety Trial	To evaluate the efficacy and safety of multiple doses of Linaclotide	Phase 3, Randomized, Double-blind, Placebo-Controlled Parallel Group	145µg Linaclotide or 290µg Linaclotide or Placebo Once daily;	Patients with Chronic Idiopathic Constipation	213 -- 145µg Linaclotide 205 -- 290µg Linaclotide 215 -- Placebo (633 total)	12 weeks

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Trial Identification Number	Type of Trial	Trial Objective	Trial Design	Trial Treatment Groups	Trial Population of Interest	Number of Enrollees	Treatment Duration
MCP-103-201	Safety, Efficacy, and Dose Response	Evaluation of dose-ranging safety, efficacy, and dose responses of multiple doses of Linaclotide	Phase 2b, Randomized, Double Blind, Placebo-Controlled, Dose-Range Finding, Parallel Group	72µg Linaclotide 145µg Linaclotide 290µg Linaclotide 579µg Linaclotide Placebo Once daily;	Patients with Chronic idiopathic constipation	59 – 72 µg Linaclotide 56 – 145 µg Linaclotide 62 – 290 µg Linaclotide 63 – 579µg Linaclotide 69 Placebo (309 total)	28 days
MCP-103-004	Safety and Pharmacodynamic	Evaluation of Safety and Pharmacodynamics of Multiple doses of Linaclotide	Phase 2a, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group	97µg Linaclotide 290µg Linaclotide 966µg Linaclotide Placebo Once daily; (liquid solution)	Patients with Chronic idiopathic constipation	12-- 97 µg Linaclotide 10 – 290 µg Linaclotide 10 – 966 µg Linaclotide 10 Placebo (42 total)	14 days

5.2 Review Strategy

Because the applicant is seeking two indications, the efficacy portion of this NDA application was divided among two clinical reviewers and statistical reviewers. Data in support of the chronic idiopathic constipation indication (CIC) was evaluated by Drs. Erica Wynn and Freda Cooner initially. Dr. Milton Fan later provided assisted with the chronic idiopathic constipation indication. Data in support of the Irritable Bowel Syndrome with Constipation indication (IBS-C) was reviewed by Drs. Lara Dimick-Santos and Milton Fan. A similar review strategy was implored for the safety portion of the application. The long-term trials were evaluated by Dr. Lara Dimick Santos.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Overview of Protocols Submitted with Application

The Linaclotide clinical development program was designed to assess the safety and efficacy of Linaclotide for the treatment of chronic idiopathic constipation and IBS-C. The entire clinical program consisted of 11 randomized, well-controlled clinical trials and two open-label long-term safety trials. The trials that were submitted in support of the Constipation Predominant IBS (IBS-C) indication were evaluated by Dr. Lara Dimick-Santos. This review will focus on the clinical trials designed to support use of the proposed product in chronic idiopathic constipation. There were six randomized, double-blind, placebo-controlled Phase 2 and Phase 3 trials submitted with this application in support of the chronic idiopathic constipation indication. The two pivotal trials conducted in support of the efficacy and safety of Linaclotide in chronic idiopathic constipation were MCP-103-303 (also referred to as MCP 303) and LIN-MD-01 (also referred to as LIN 01). The designs of the individual CIC Phase 3 trials are summarized in the tables and schematics below.

Table 3 Reviewers Summary of Trial Design Trial LIN-MD-01

Study # and Period	LIN-MD-01 under IND 63,290 (October 10, 2008 – July 16, 2009) Original Protocol Date: August 19, 2008
<i>Design</i>	Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-dose, Multi-centered (103 centers – 95 US and 8 Canada)
<i>Primary Objectives</i>	To determine the efficacy and safety of Linaclotide administered to patients with chronic idiopathic constipation
<i>Treatments[±]</i>	Linaclotide 133µg (150µg) daily or Linaclotide 266µg (300 µg) daily or Placebo Treatments are taken once daily in the morning at least 30 minutes before breakfast for 12 weeks.
<i>Sample Patient Population</i>	Adult (aged 18 years or older) male and female outpatients with a diagnosis of Chronic idiopathic constipation (using Modified Rome II criteria) who meet required bowel movement criteria during the pretreatment period. <div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">Key Inclusion Criteria</div> <ul style="list-style-type: none"> • Meet the colonoscopy requirements defined by the American Gastroenterological Association guidelines. • No clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests after signing the ICF but before receiving the first dose of study drug. The investigator will determine if a particular finding is clinically significant. • Meet modified Rome II criteria – patient reports fewer than three bowel movements (BMs) per week (with each BM occurring in the absence of any laxative, suppository, or enema use during the preceding 24 hours) and reports one or more of the following symptoms for at least 12 weeks, which need not be consecutive, in the 12 months before the Screening Visit or before starting chronic treatment with tegaserod, lubiprostone, polyethylene glycol 3350, or any laxative: <ul style="list-style-type: none"> ○ Straining during more than 25% of bowel movements ○ Lumpy or hard stools during more than 25% of bowel movements ○ Sensation of incomplete evacuation during more than 25% of bowel movements. • Report an average of fewer than 3 CSBMs per week and 6 or fewer SBMs per week by the IVRS during the 14 days before the start of treatment period. <ul style="list-style-type: none"> ○ CSBM = an SBM that is associated with a sense of complete evacuation ○ SBM = 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 • Be willing to discontinue any laxative use before the Screening visit in favor of the protocol-defined rescue medicine (bisacodyl tablets or bisacodyl suppositories) <div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">Key Exclusion Criteria</div> <ul style="list-style-type: none"> • Report loose (mushy) or watery stools (BSFS score of 6 or 7) in the absence of any laxative, suppository, enema, or prohibited medicine for more than 25% of BMs during the 12 weeks before the Screening Visit • Meet the Rome II criteria for Irritable Bowel Syndrome: reports abdominal discomfort or pain that has two or more of the following three features for at least 12 weeks, which need not be consecutive, in the 12 months before the Screening Visit: <ul style="list-style-type: none"> ○ Relieved with defecation ○ Onset associated with a change in frequency of stool ○ Onset associated with a change in form (appearance) of stool • Have a structural abnormality of the GI tract or a disease or condition that can affect GI motility. • Have ever had a diagnosis of familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, or any other form of familial colorectal cancer or inflammatory bowel disease. Has a family history of familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer or other familial form of colorectal cancer. • Have currently unexplained and clinically significant alarm symptoms (lower GI bleeding, iron deficiency anemia, weight loss) or systemic signs of infection or colitis • Have currently active peptic ulcer disease that is not adequately treated or stable with therapy • Have a history of diverticulitis or any chronic condition (e.g. chronic pancreatitis, polycystic kidney disease, ovarian cysts, endometriosis) that can be associated with abdominal pain or discomfort and could confound the assessments in this trial

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	<ul style="list-style-type: none"> • Have potential CNS cause of constipation (e.g. Parkinson’s disease, spinal cord injury, multiple sclerosis) • Have ever had 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 • History of fecal impaction that required hospitalization or emergency room treatment or have a history of cathartic colon, laxative, or enema abuse, ischemic colitis, or pelvic floor dysfunction (unless successful treatment has been documented by a normal balloon expulsion test). • History of major surgery 30 days before the screening visit; appendectomy or cholecystectomy 60 days before the screening visit; abdominal, pelvic, or retroperitoneal surgery 6 months before the Screening Visit; bariatric surgery or surgery to remove a segment of the GI tract at any time before the screening visit. • History of diabetic neuropathy • History of cancer other than basal cell or squamous cell carcinoma of the skin. Patients with cancer history allowed provided that cancer has been in complete remission for at least 5 years before the Randomization Visit. • Have hypothyroidism that is being treated and for which the dose of thyroid hormone has not been stable for at least 6 weeks at the time of Screening • Report a BSFS score of 6 (loose, mushy stools) for more than 1 SBM or a BSFS score of 7 (watery stools) with any SBM during the 14 days before the start of the treatment period. • Have been hospitalized for a psychiatric condition or have made a suicide attempt during the 2 years before the Randomization Visit. • Have been randomized into any Phase I or Phase II study in which Linaclotide was a treatment (patients who enrolled into these studies but failed to be randomized are eligible for the current trial) or have previously entered the pretreatment period of this trial or any other phase III trial in which Linaclotide was a treatment.
<i>Number Planned (Number Enrolled)</i>	600 Planned Approximately 633 Randomized 215 Placebo 213 Linaclotide 133 µg (150µg) daily 205 Linaclotide 266 µg (300µg) daily 533 Completed Trial
<i>Efficacy Assessments</i>	Interactive voice response system (IVRS) information that determines whether a BM is a complete spontaneous bowel movement (CSBM). Interactive voice response system (IVRS) questions that determine the following: <ul style="list-style-type: none"> • Whether a BM is a spontaneous bowel movement (SBM) • Stool consistency (Bristol Stool form Scale [BSFS]) • Severity of straining • Weekly patient assessment of constipation severity • Daily patient assessment of abdominal discomfort • Daily patient assessment of bloating
<i>Primary Efficacy Parameters</i>	12-week complete spontaneous BM (CSBM) Overall Responder <ul style="list-style-type: none"> • CSBM overall responder = patient who was a CSBM weekly responder for ≥ 9 of the 12 weeks of the Treatment Period • CSBM weekly responder = CSBM frequency rate ≥ 3 with an increase from baseline of ≥ 1 If a patient does not have CSBM frequency data for a particular treatment period week, the patient will not be considered a CSBM weekly responder for that week.
<i>Key Secondary Efficacy Parameters</i>	<ul style="list-style-type: none"> • Change from baseline in 12-week CSBM frequency • Change from baseline in 12-week SBM frequency

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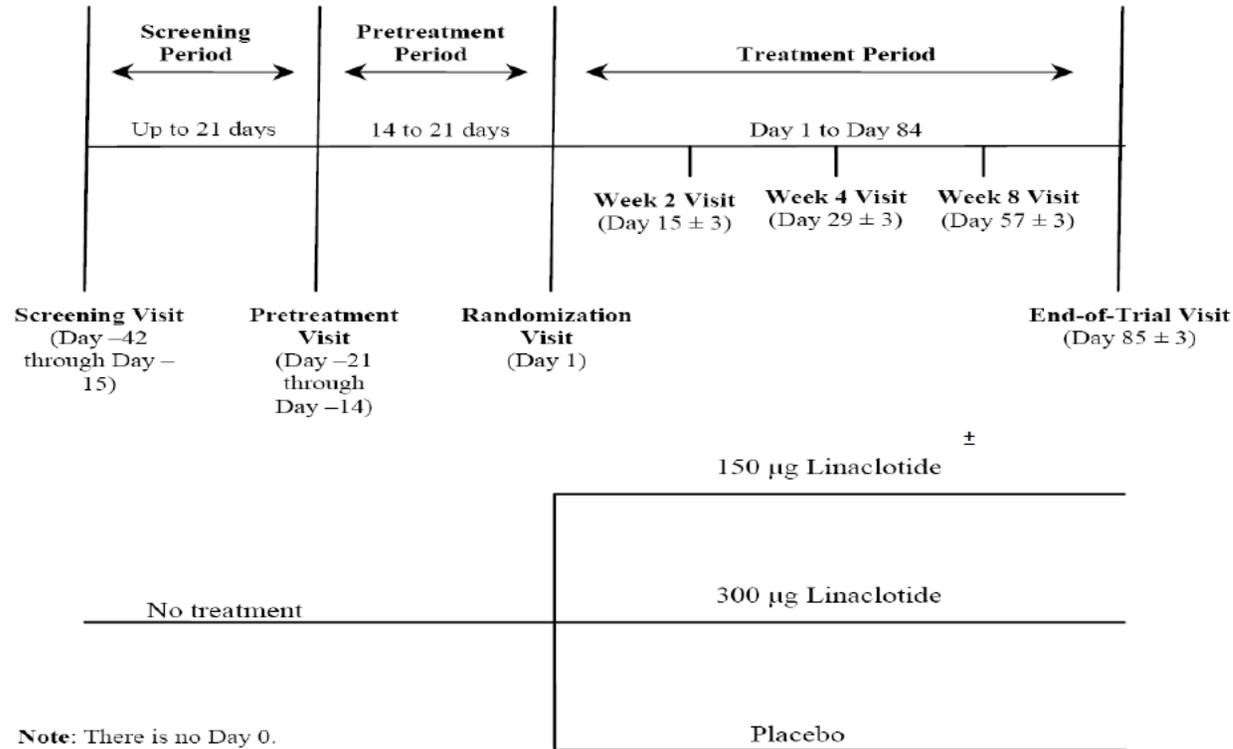
Study # and Period	LIN-MD-01 under IND 63,290 (October 10, 2008 – July 16, 2009) Original Protocol Date: August 19, 2008
	<ul style="list-style-type: none"> • Change from baseline in 12-week stool consistency • Change from baseline in 12-week severity of straining • Change from baseline in 12-week constipation severity • Change from baseline in 12-week abdominal discomfort • Change from baseline in 12-week bloating.
Safety Data	Adverse event recording, clinical laboratory measures, vital sign parameters, and electrocardiograms (ECGs)
Protocol Amendment 1	Amended December 18, 2008 <ul style="list-style-type: none"> • Addition of separate sections to clearly identify assessments and statistical analyses that are related to Health Outcomes Assessments • Addition of pharmacokinetic (PK) sample and triplicate ECG collection at various study visits fro approximately 150 – 175 patients • Update to the Introduction with additional epidemiological and chronic idiopathic constipation treatment information. • Revision of Inclusion criteria #6 to clarify urine drug screen requirements • Revision of Inclusion criteria #10 to clarify the timing of patient use of protocol-defined rescue medication in the Pretreatment Period • Revision of Exclusion criteria #20 to make clear that no investigational drug except the investigational drug of this trial (Linaclotide) is acceptable during participation in the trial. • Clarification of Randomization (Visit 3) sequence of study procedures • Clarification of allowed use narcotics as part of the colonoscopy procedure • Clarification of the data utilized to calculate the sample size • Minor corrections to the protocol for editorial and grammatical purposes.
Protocol Amendment 2	Amended October 7, 2009 <ul style="list-style-type: none"> • Updates to the statistical analyses of the primary, secondary, and additional efficacy parameters <ul style="list-style-type: none"> ○ For the primary and secondary efficacy parameters, subgroup analyses based on gender and age groups (≥ 65 vs. < 65) will be performed in the future Integrated Summary of Efficacy using the integrated efficacy data from the controlled pivotal efficacy studies for Chronic idiopathic constipation ○ The Mantel-Haenszel estimate of odds ratio (controlling for geographic region) and the corresponding 95% confidence interval for each Linaclotide dose group over placebo group will also be provided for the primary efficacy parameter in addition to the Cochran-Mantel Haenszael test results ○ Language amended so that change from baseline in CSBM frequency rate and SBM frequency rate will be calculated ○ Edits in the description of the secondary efficacy parameters ○ 12 additional efficacy parameters added to the protocol <ul style="list-style-type: none"> ▪ BM within 24 hours of receiving the first dose of study drug ▪ Change from baseline in 12 week abdominal pain ▪ Complete Spontaneous Bowel Movement Weekly Responder (a weekly CSBM responder for that week if the CSBM weekly frequency rate is 3 or greater and increased by 1 or more from baseline.) ▪ 12 week constipation responder ▪ Treatment Period CSBM Rate Change ≥ 1 Responder ▪ 12 week CSBM Rate ≥ 3 Responder

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Study # and Period	LIN-MD-01 under IND 63,290 (October 10, 2008 – July 16, 2009) Original Protocol Date: August 19, 2008
	<ul style="list-style-type: none"> ▪ 12 week CSBM Rate Change \geq 1 Responder ▪ 12 week SBM Responder ▪ 12 week Stool Consistency Responder ▪ 12 week Severity of Straining Responder ▪ 12 week Constipation Severity Responder ▪ 12 week Abdominal Discomfort Responder ▪ 12 week Bloating Responder <ul style="list-style-type: none"> • Updates to the statistical analyses of health outcome parameters <ul style="list-style-type: none"> ○ Description of the EQ-5D assessment edited. EQ-5D is a generic measure of health status used in Europe • Additional language added to clarify the presentation of results related to adverse events reported during the study (The TEAEs will be summarized by treatment group and overall Linaclotide group ((i.e. the total of the 150μg and 300μg Linaclotide groups)

± Changes in the analytical procedures resulted in changes in the dose-strength expression. (see Section 6.1.8) The dose strengths of 150 μ g and 300 μ g used in the protocols are analogous to the 133 μ g and 266 μ g used in the clinical study report and the final 145 μ g and 290 μ g doses proposed by the applicant. for commercial use. Linaclotide doses in this trial reflect the total peptide content.

Figure 1 Schematic of Trial LIN-MD-01



Note: There is no Day 0.

Note: ± Changes in the analytical procedures resulted in changes in the dose-strength expression. (see Section 6.1.8) The dose strengths of 150µg and 300µg used in the protocols are analogous to the final 145µg and 290µg doses proposed by the applicant for commercial use.. Linaclotide doses in this trial reflect the total peptide content.

Source: Applicant's Clinical Study Report Trial LIN-MD-01 p 52 of 3903

Table 4 Schedule of Assessments Trial LIN-MD-01

	Screening Period (Up to 21 days)	Pretreatment Period (14-21 days)	Treatment Period (12 weeks)				
Visit	Screening Visit	Pretreatment Visit	Randomization Visit	Week 2	Week 4	Week 8	EOT Visit Week 12 ^a
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Trial Day	Day -42 through Day -15	Day -21 through Day -14	Day 1	Day 15 ± 3	Day 29 ± 3	Day 57 ± 3	Day 85 ± 3
Informed consent	X						
Inclusion and exclusion criteria verification	X	X	X				
IVRS registration ^b	X	X	X				X
Medical and surgical history	X						
Physical examination ^c	X						X
Body weight and height ^d	X	X	X	X	X	X	X
Seated vital signs ^e	X	X	X	X	X	X	X
12-Lead ECG	X						X
Prior and concomitant medicines	X	X	X	X	X	X	X
Clinical laboratory determinations ^f	X		X		X		X
Pregnancy test ^g	X		X		X		X
Laxative, suppository, and enema washout instructions ^h	X						
AE evaluations ⁱ		X	X	X	X	X	X
IVRS training or IVRS compliance verification and reminder ^j		X	X	X	X	X	
Rescue medicine dispensed ^k		X	X	X	X	X	
Randomization			X				
Patient IVRS call, in clinic			X				
PAC-QOL questionnaire			X				X
EQ-5D questionnaire			X	X	X	X	X
HRUQ			X		X	X	X
SF-12			X	X	X	X	X
WPAI:C			X		X	X	X

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	Screening Period (Up to 21 days)	Pretreatment Period (14-21 days)	Treatment Period (12 weeks)				
Visit	Screening Visit	Pretreatment Visit	Randomization Visit	Week 2	Week 4	Week 8	EOT Visit Week 12 ^a
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Treatment-satisfaction assessment				X	X	X	X
Rome III status			X				
Study drug dispensed			X		X	X	
Study drug administration ⁱ			X				
Study drug accountability					X	X	X
Treatment-continuation assessment							X

Source Applicant's Table Clinical Study Report LIN-MD-01 pp 28 - 31 of 3903

a Patients who are randomized but do not complete the treatment period (withdraw consent or are discontinued before they have completed 12 weeks of treatment) shall be considered treatment-period withdrawals and should complete the procedures required at the EOT Visit (even out of window).

b Trial Coordinator should call IVRS to transition the patient to the next appropriate trial period. Refer to the IVRS Center User Manual.

c A physical examination should include the following: general appearance, HEENT (head, ears, eyes, nose, and throat), neck, cardiovascular, thorax/lungs, abdomen, musculoskeletal, lymph nodes, skin, and neurologic and mental status. A rectal examination should be performed during the screening period on all patients who do not require a colonoscopy. After the screening period, the rectal examination is optional and may be performed at the discretion of the Investigator. Breast and genitourinary examinations are optional at the discretion of the Investigator.

d Height will only be measured at Visit 1 (Screening).

e Vital signs (oral temperature, respiratory rate, systolic and diastolic blood pressure, and pulse rate) must be obtained from patients who are in the seated position.

f Complete blood count, chemistry, urinalysis, and urine drug screen. The drug screen will be performed only at the Screening Visit (Visit 1).

g To be eligible to continue in the trial, a negative serum pregnancy test must be documented at the Screening Visit (Visit 1) and at Week 4 (Visit 5). A negative urine pregnancy test must be documented at the Randomization Visit (Visit 3) before dosing and at the EOT Visit (Visit 7).

h Trial Coordinator will instruct patients about the use of laxatives, suppositories, and enemas (refer to Appendix II, Concomitant Medicines).

i All AEs occurring after the patient signs the informed consent form will be documented.

j At Visit 2 (pretreatment), the Trial Coordinator will instruct the patients about the use of the IVRS. At subsequent visits, the Trial Coordinator will access the IVRS to verify patient compliance with the daily IVRS call requirement. After determining the patient's compliance, the Trial Coordinator will remind patients to call the IVRS daily. (IVRS questions may be found in the IVRS Center User Manual [refer to Efficacy Measurements, Section 9.5.2]).

k Rescue medicine (bisacodyl tablets or bisacodyl suppositories) will be supplied to patients at Visit 2 (pretreatment) and, if needed, at subsequent visits.

l Study drug will be administered in the clinic at the Randomization Visit (Visit 3) (study drug does not need to be taken in the morning before breakfast). On all other days, study drug will be taken once daily in the morning at least 30 minutes before breakfast. Patients will not take study drug on the morning of the EOT Visit (Visit 7). Patients are instructed to fast 2 hours before the Randomization Visit (Visit 3) and EOT Visit (Visit 7).

AE = adverse event; ECG = electrocardiogram; EOT = end of trial; EQ-5D = EuroQoL-5D; HRUQ = Health Resource Use Questionnaire; IVRS = interactive voice response system; PAC-QOL = Patient Assessment of Constipation Quality of Life questionnaire; SF-12 = Short Form-12 Health Survey; WPAI:C = Work Productivity and Activity Impairment Questionnaire for Constipation.

Table 5 Reviewers Summary of Trial MCP-103-303

Study # and Period	MCP-103-303 (August 20, 2008 – August 12, 2009)
<i>Design</i>	12-week Phase 3, Randomized, Double Blind, Placebo-Controlled, Parallel-group, Multi-centered Multi-dose Trial Followed by a 4-Week Randomized Withdrawal Period (103 centers in the United States)
<i>Primary Objective</i>	To determine the efficacy and safety of Linaclotide administered to patients with chronic idiopathic constipation
<i>Treatments[±]</i>	<p>Treatments are taking once daily in the morning at least 30 minutes before breakfast for 12 weeks.</p> <p>150 µg Linaclotide 300 µg Linaclotide Placebo</p> <p>(Note: The dose strengths of 150µg and 300µg used in the protocols are analogous to the 133µg and 266µg used in the clinical study report and the final 145µg and 290µg doses proposed by the applicant for the commercial product. Linaclotide doses in this trial reflect the total peptide content.</p>
<i>Sample Patient Population</i>	<p>KEY INCLUSION CRITERIA</p> <p>*Male and females ≥ 18years if they meet the following criteria for Chronic idiopathic constipation (adapted from Rome II Criteria for Functional Constipation)</p> <ul style="list-style-type: none"> • < 3 Spontaneous Bowel Movements (SBMs)per week and had 1 of the following symptoms for at least 12 weeks (which need not be consecutive, in the preceeding 12 months) <ul style="list-style-type: none"> ○ Straining during >25% of Bowel Movements ○ Lumpy or hard stools during > 25% of Bowel Movements ○ Sensation of incomplete evacuation during >25% of Bowel Movement <p>Patients meeting the above criteria were eligible if during the 14 day Pre-Treatment Period, they reported < 3 complete spontaneous bowel movements (CSBMs) per week and ≤ 6 SBMs per week and were compliant with interactive voice response system completion. (CSBM = SBM that is associated with a sense of complete evacuation. SBM = a BM that occurs in the absence of laxative, suppository, or enema use on the calendar day of (or before) the BM.</p> <p>*Patient met colonoscopy requirements according to American Gastroenterological Association (AGA) Guidelines *Patient agreed to reframe from making any new, major lifestyle changes that might have affected Chronic idiopathic constipation Symptoms.</p> <p>KEY EXCLUSION CRITERIA</p> <p>Patients were excluded for any of the following reasons:</p> <ul style="list-style-type: none"> • Patient report of Loose (mushy) stools for >25% of their BMs during the 12 weeks before the Screening Visit • Meeting the Rome II criteria for Irritable Bowel Syndrome • During the Pre-Treatment Period, patient reported a Bristol Stool Form Scale (BSFS) score of 7 for any SBM or a BSFS score of 6 for more than 1 SBM • Study Participant Used Rescue Medication (bisacodyl tablet or suppository) or any other laxative, suppository or enema on the calendar day before ore the calendar day of the start of the Treatment Period (i.e. before the Randomization Visit). • Structural Abnormality of the GI tract or disease or condition that might have affected GI motility • Prior diagnosis of familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer or any other form of familial colorectal cancer or inflammatory bowel disease. • Patient had family history of familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer or other familial form of colorectal cancer. • Patient had active peptic ulcer disease

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Study # and Period	MCP-103-303 (August 20, 2008 – August 12, 2009)
	<ul style="list-style-type: none"> • Patient had history of diverticulitis or any chronic condition • Patient currently had unexplained clinically significant alarm symptoms on physical exam or systemic signs of infection or colitis • Patient had a potential central nervous system cause of constipation • Patient had any of the predefined diseases or conditions that could have been associated with constipation • Patient had ever had fecal impaction that required hospitalization or emergency room treatment or had a history of a cathartic colon, laxative, or enema abuse, ischemic colitis, or pelvic floor dysfunction • Patient met any of the predefined surgery criteria. • Patient had a history of cancer other than treated basal cell or squamous cell carcinoma of the skin. (Patients with a history of cancer were allowed provided that the malignancy had been in complete remission for ≥ 5 years before the Randomization visit.) • Patient had a history of diabetic neuropathy • Patient had treated hypothyroidism for which the dose of thyroid hormone had not been stable for ≥ 6 weeks • Patient had been randomized into any Phase 1 or Phase 2 study in which Linacotide was a treatment (patients who enrolled into Phase 1 or Phase 2 studies but failed to be randomized were eligible) or had previously entered the Pretreatment Period of this trial or any other Phase 3 trial in which Linacotide was a treatment
<i>Number Planned (Number Enrolled)</i>	600 Planned Approximately 643 Randomized 209 Placebo 217 Linacotide 133 µg/day 217 Linacotide 266 µg/day 540 Randomized for Withdrawal Phase
<i>Efficacy Assessments</i>	Daily assessments of IVRS information that determines whether a BM is a CSBM. Daily IVRS assessments of <ul style="list-style-type: none"> • Daily Bowel Movements • Daily Patient Symptom Severity Assessments • Use Per-protocol Rescue Medicine of Any other Laxatives, Suppositories, or Enemas Weekly IVRS assessments of <ul style="list-style-type: none"> • Weekly Patient Assessment of Constipation Severity • Weekly Patient Assessment of Degree of Relief of Constipation Symptoms The following will also be captured during the Treatment Period <ul style="list-style-type: none"> • Euro-Quality of Life • Short Form 12 Health Survey • Health Resource Use Questionnaire • Work Productivity and Activity Impairment Questionnaire Chronic Constipation • Patient Assessment of Constipation Quality of Life Questionnaire • Treatment Satisfaction Assessment Treatment Continuation Assessment

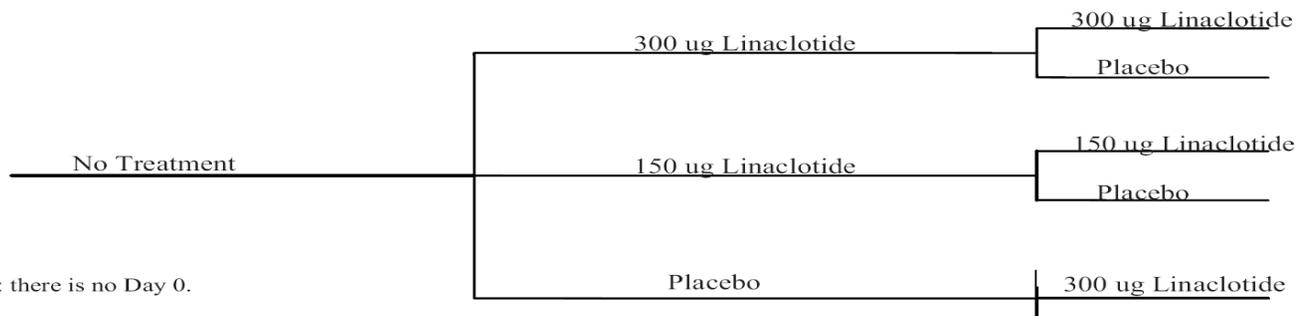
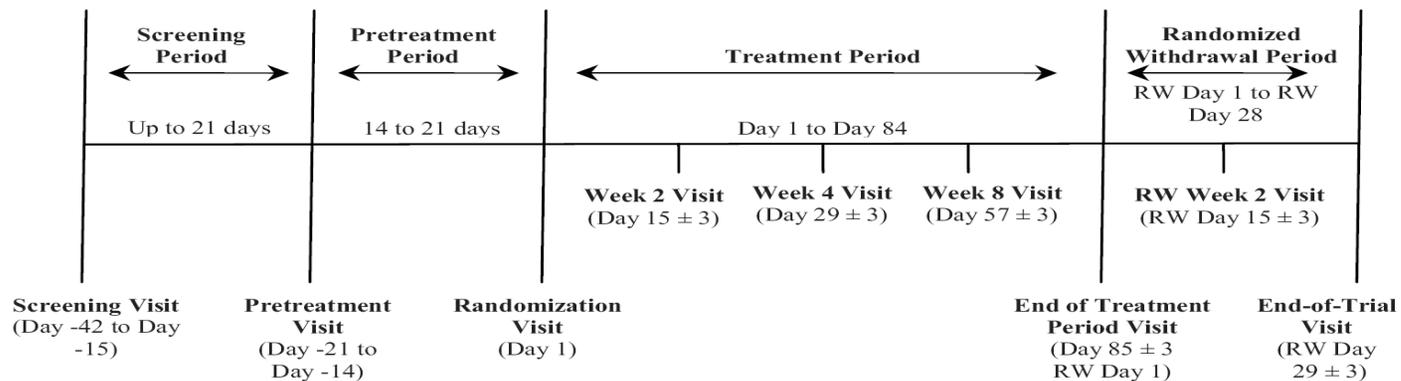
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Study # and Period	MCP-103-303 (August 20, 2008 – August 12, 2009)
<i>Primary Efficacy Parameters</i>	12-week complete spontaneous BM (CSBM) Overall Responders during the first 12 weeks of Treatment in the Treatment Period. <ul style="list-style-type: none"> • CSBM overall responder = patient who was a CSBM weekly responder for ≥ 9 of the 12 weeks of the Treatment Period • CSBM weekly responder = CSBM rate ≥ 3 with an increase from baseline of ≥ 1 CSBM
<i>Key Secondary Efficacy Parameters</i>	Change in Baseline in 12-week CSBM Frequency Rate Change in Baseline in 12-week SBM Frequency Rate Change in Baseline in 12-week Stool Consistency Change in Baseline in 12-week Severity of Straining Change in Baseline in 12-week Abdominal Discomfort Change in Baseline in 12-week Bloating Change in Baseline in 12-week Constipation Severity
<i>Additional Efficacy Parameters</i>	BM (CSBM [SBM]) Within 24 hours of Receiving the First Dose of Study Drug Change from Baseline in 12-Week Abdominal Pain Complete Spontaneous Bowel Movement weekly Responder 12 week Constipation Responder Treatment Period CSBM Rate Change ≥ 1 Responder 12 week CSBM Rate ≥ 3 Responder 12-week CSBM Rate Change ≥ 1 Responder 12-week SBM Responder 12-week Stool Consistency Responder 12-week Severity of Straining Responder 12-week Constipation Severity Responder 12-week Abdominal Discomfort Responder 12-week Bloating Responder 12-week Degree of Global Relief of Constipation Symptoms Responder Use of Per-Protocol Rescue Medicine or Any Other Laxative, Suppository, or Enema Treatment Satisfaction Treatment Continuation
<i>Safety Data</i>	Safety Assessments included adverse events, vital signs, electrocardiograms, clinical laboratory measurements and physical examinations
<i>Protocol Amendment 1</i>	Amended November 21, 2008 Inclusion criteria #6 was clarified to indicate that the Investigator was to determine the clinical significance of a positive urine drug screen Inclusion criteria #10 was clarified to require use of protocol-defined rescue medications Exclusion criteria #20 was clarified to exclude any other investigational drug other than the Linaclotide administered in this trial. Clarification provided on study drug dosing, sequence of events, and logistics on specified trial visits. Clarification provided on return of all unused study drug capsules Changes were made to the schedule for collection of urine and serum for pregnancy tests to ensure timely results over the course of the trial Clarification provided on randomization and dosing during the Randomized Withdrawal Period New sections were created for health outcomes assessments and parameters Sensitivity analysis was removed and provided in the Statistical Analysis Plan

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Study # and Period	MCP-103-303 (August 20, 2008 – August 12, 2009)
	<p>Triplicate ECGs and PK sampling was included for a subset of patients to complete adequate premarketing investigation of Linaclotide for effects on QT/QTc. Appendix X was added and related were updated to accommodate these additional assessments Clarifications were added when necessary and editorial errors were corrected</p>
<i>Protocol Amendment 2</i>	<p>Amended October 07, 2009</p> <ul style="list-style-type: none"> • Subgroup analyses by gender and age were specified for inclusion in the future Integrated Summary of Efficacy • Efficacy analyses was updated to reflect the analyses and methods specified in Version 2 of the SAP • Health Outcomes Parameters, was updated to reflect the analyses and methods specified in the Health Economics and Outcome Research • Safety Analyses was updated to reflect AE and clinical laboratory parameter summaries specified in Version 2 of the Statistical Analysis Plan • Clarifications were added when necessary.

Figure 2 Schematic Overview of Trial Design MCP-103-303



Note: there is no Day 0.
 RW= Randomized Withdrawal

Note: Total Linaclotide content doses of 133µg and 266µg correspond to total peptide content of 150µg and 300µg respectively. The final Linaclotide dose expressions were 145µg and 290µg respectively
 Source: Applicants Clinical Study Report Trial MCP-103-303 p.2042 of 4032

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Table 6 Schedule of Assessments Trial MCP-103-303

	Screening Period (Up to 21 days)	Pretreatment Period (14 to 21 days)	Treatment Period (12 weeks)				Randomized Withdrawal (RW) Period (4 weeks)		
Visit Days	Screening Visit (Day -42 to Day -15)	Pretreatment Visit (Day -21 to Day -14)	Randomization Visit (Day 1)	Week 2 Visit (Day 15 ± 3)	Week 4 Visit (Day 29 ± 3)	Week 8 Visit (Day 57 ± 3)	End of Treatment Period Visit (Day 85 ± 3; RW-Day 1)	RW Week 2 Visit (Day 15 ± 3)	End-of-Trial Visit Follow-up (Day 29 ± 3)
Visit Numbers	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Trial Procedures									
Inclusion and Exclusion Criteria Verification	X	X	X						
Signature of ICF	X								
IVRS Registration	X	X	X				X		X
Medical History	X								
Physical Examination ^b	X						X		X
Body Weight and Height ^c	X	X	X	X	X	X	X	X	X
Seated Vital Signs ^d	X	X	X	X	X	X	X	X	X
12-Lead ECG	X						X		X
Prior and Concomitant Medicines	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests ^e	X		X		X		X		X
Pregnancy Test ^f	X		X		X		X		X
Laxative/Suppository/Enema/ Washout Instructions ^g	X								
AE Evaluations ^h		X	X	X	X	X	X	X	X
IVRS Training/IVRS Compliance Verification &Reminder ⁱ		X	X	X	X	X	X	X	
Rescue Medicine Dispensed ^j		X	X	X	X	X	X	X	
Patient IVRS Call, in Clinic			X				X		
Randomization			X				X		
PAC-QOL			X				X		X
EQ-5D			X	X	X	X	X	X	X
Rome III Status			X						

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HRUQ			X		X	X	X		X
SF-12 Health Survey			X	X	X	X	X	X	X
WPAI:C			X		X	X	X		X
Treatment Satisfaction Assessment				X	X	X	X	X	X
Study Drug Dispensed			X		X	X	X		
Study Drug Administration			X				X		
Study Drug Accountability					X	X	X		X
Treatment Continuation Assessment							X		X

Source: Applicants Clinical Study Report Trial MCP-103-303 pp. 2053 – 2054 of 4032

a Trial coordinator to call IVRS to transition the patient to the next appropriate trial period. Refer to the IVRS User Manual.

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

c Height is measured only at the Screening Visit.

d Vital signs must be obtained in the seated position and include oral temperature, respiratory rate, blood pressure, and pulse.

e Chemistry, CBC, UA, and drug screen. The drug screen will be performed at the Screening Visit only.

f To be eligible to continue in the trial, a negative serum pregnancy test must be documented at the Screening, Week 4, and ETP Visits. A negative urine pregnancy test must be documented at the Randomization Visit prior to dosing. A negative urine pregnancy test must also be documented at the EOT Visit.

g Trial coordinator will instruct patients about the use of laxatives, suppositories, and enemas.

h All AEs occurring after the patient signs the ICF will be captured.

i At the Pretreatment Visit the trial coordinator will instruct the patients about the use of the IVRS system. At subsequent visits the trial coordinator will access the IVRS system to verify patient compliance with the daily IVRS call requirement. After determining the patient's compliance, the trial coordinator will remind patients to call the IVRS daily. (IVRS questions may be found in the IVRS User Manual [refer to Efficacy Measurements, Section 9.5.2])

j Rescue medicine (oral bisacodyl or bisacodyl suppositories) will be supplied to patients at the Pretreatment Visit and, if needed, at subsequent visits. on Page 41 StudyMCP-103-303-P1 10 July 2008

k Study drug will be administered in the clinic at the Randomization and ETP Visits (study drug does not need to be taken in the morning before breakfast).. Patients are instructed to fast 2 hours before these clinic visits. On all other days, study drug will be taken once daily in the morning at least 30 minutes before breakfast. Patients will not take study drug on the mornings of the ETP and EOT Visits.

l Patients who are randomized but do not complete the Treatment Period or RW Period (withdraw consent or are discontinued before they have completed 12 weeks or 4 weeks of treatment, respectively), shall be considered Treatment Period or RW Period withdrawals and should complete the procedures required at the EOT Visit (even out of window).

5.3.2 Clinical Overview of Results of Trial LIN-MD-01

Additional integrated information may be found in Section 6 of this review. Trial LIN-MD-01 was a Phase 3, Randomized, Double-blind, Parallel Group, Placebo-Controlled trial assessing two doses of Linaclotide (145µg and 290µg) administered once daily orally for 12 weeks in patients with chronic idiopathic constipation (CIC). The results of Trial LIN-MD-01 demonstrated that both the 145µg and 290µg doses of Linaclotide were more effective than placebo at achieving the primary outcome endpoint (CSBM overall responder). (Note: A 12-week CSBM Overall Responder was a subject 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. The modified definition of CSBM overall responder required a patient to have at least 4 days of IVRS data. See Section 5.3.2.1 for additional information.) The overall response rate was 5.6% in the placebo group, 15.5% in the Linaclotide145µg group and 20.3% in the Linaclotide290 µg group using the modified definition of a 12 week overall CSBM responder. The trial was not designed to assess superiority (or noninferiority) in efficacy between the two Linaclotide doses. Results for the primary outcome parameter were statistically significant. Statistically significant differences were also seen in the secondary endpoints, which included changes from baseline in 12 week- CSBM frequency, SBM frequency, stool consistency, severity of straining, constipation severity, abdominal discomfort and bloating.

The incidence of treatment emergent adverse events (TEAE) was similar across treatment groups, with the exception of diarrhea. Diarrhea was the most frequently reported TEAE in both of the Linaclotide groups (19.7% in the 145µg group and 14.6% in the 290µg group vs. 2.8% in the placebo group.). More patients in the Linaclotide groups discontinued the trial because of diarrhea (5.3% Linaclotide groups combined vs. 0.5% placebo). Patients in the 290µg Linaclotide group experienced a higher percentage of serious and severe adverse events than the other two treatment groups.

The following is a review of the results from Trial LIN-MD-01. (Note: Changes in analytical procedures resulted in changes in the dose-strength expression for the proposed drug product. The dose strengths of 150µg and 300µg used in the protocols are analogous to the 133µg and 266µg used in the clinical study report and the 145µg and 290µg doses in the final labeling submitted by the applicant. The final 145µg and 290µg doses proposed by the applicant as Linaclotide doses for use in the commercial product reflect the total Linaclotide content. Throughout the review of this trial the doses of 145µg and 290µg are used. The reader is referred to Section 6.1.8 of this review for additional information.)

5.3.2.1 Results of 12- Week Treatment Period of Trial LIN-MD-01

A total of 5 patients randomized in LIN-MD-01 were previously randomized in another clinical trial of Linaclotide, in violation of the protocol. The applicant developed rules for inclusion of the data from duplicate patients in the efficacy and safety analyses. These rules are outlined in Section 7.1 of this review. The reader is referred to the statistical review of Dr. Milton Fan. Duplicate patients are listed in the table below.

Table 7 Duplicate Patients Trial LIN-MD-01

LIN-MD-01 Patient ID Number	Duplicate Patient ID Number (Second Study ID)	Treatment Group	Description of Deviation
0050101	041016 (MCP-103-201)	Linaclotide290 ug	Patient was previously randomized under another patient I.D. in another 2b Linaclotide trial. Because of this, patients met exclusion criterion #22 of the protocol.
0160101	281002 (MCP-103-202)	Linaclotide145 ug	
0760101	244032 (MCP-103-202)	Linaclotide145 ug	
0880114	003019 (MCP-103-201)	placebo	
0950112	244005 (MCP-103-202)	Linaclotide290 ug	

There were 1232 patients screened to enter the trial. A total of 103 trial centers enrolled 633 patients (Placebo: 215 patients; Linaclotide145 µg: 213 patients; Linaclotide290 µg: 205 patients). Patient populations are presented by treatment group in the Table below.

Table 8 Patient Populations Trial LIN-MD-01

Patients Screened = 1232				
Screen Failures = 274				
Pretreatment Failures = 325				
	Placebo	Linaclotide		Total
		145µg	290µg	
Patients Randomized	215	213	205	633
Safety Population	215	213	205	633
Intent-to-Treat Population	215	213	202	630
Study Completers	191	173	169	533

Source: Reviewers Table generated from JMP ADSL dataset with additions from Table 14.1.2 Clinical Study Report LIN-MD-01 page 168 and Table 11.1 Clinical Study Report LIN-MD-01 page 83.

The dose strengths of 150µg and 300µg used in the protocols are analogous to the final 145µg and 290µg doses expressed in this table and proposed by the applicant.

Approximately 22% (274/1232) of the patients screened, were screen failures. This may ultimately impact the generalizability of the study results to the larger U.S. population. Of the

274, patients who failed screening, 186 (68%) did not meet inclusion/exclusion criteria. Eighty three percent (83%) of the pretreatment failures did not meet inclusion/exclusion criteria. Of the 633 patients enrolled, 630 (99.5%) were included in the intent-to-treat (ITT) population and 533 (84%) completed the trial. By protocol definition, the ITT population consisted of all patients in the safety population who had at least 1 post-randomization entry of the primary efficacy assessment (i.e. the daily IVRS information that determined whether a SBM is a CSBM). The safety population was defined as all patients who had a screening visit and were assigned a PID number (Visit 1); were randomized to a treatment group at the Randomization visit (Visit 3); and received at least 1 dose of the double-blind trial medication during the treatment period.

The majority of patients enrolled in the trial were female, white, and non-Hispanic. Baseline demographics were fairly consistent across treatment arms and there did not appear to be any meaningful differences among the treatment arms in race, gender, ethnicity, and BMI. There was a small numerically higher percentage of patients enrolled in the placebo arm (relative to the other treatment arms) who were over the age of 65 years (12.6% placebo; 11.3% 145µg Linaclotide, 10.4% 290µg Linaclotide). However, the mean ages were comparable across treatment groups (47 years placebo; 48.5 years 145µg Linaclotide; 47.3 years 290µg Linaclotide). Because each of the trial arms enrolled a small percentage of patient over the age of 65 years, the study may not truly represent the real world patient population. As stated previously, a risk factor for developing chronic idiopathic constipation is older age. Summaries of demographic and baseline characteristics are based on the ITT population and presented in the table below.

Table 9 Demographics of ITT Population Trial LIN-MD-01

Characteristic	TRIAL LIN-MD-01		
	PLACEBO N = 215	LIN 145µg N = 213	LIN 290µg N = 202
Age (years):			
Mean (standard deviation)	47.0 (13.5)	48.5 (12.3)	47.3 (13.0)
Median	47	48	47
Min, Max	20, 76	20, 83	20, 82
Age Group in years n(%)			
18 < 40:	64 (29.7%)	49 (23%)	58 (28.7%)
40 < 65:	124 (57.7%)	140 (65.7%)	123 (60.9%)
≥ 65:	27 (12.6%)	24 (11.3%)	21 (10.4%)
Sex n(%)			
Male	19 (8.8%)	18 (8.5%)	23 (11.4%)
Female	196 (91.2%)	195 (91.5%)	179 (88.6%)
Race n(%)			
White	168 (78.1%)	168 (78.9%)	152 (75.2%)
Black	42 (19.5%)	41 (19.2%)	46 (22.8%)
Asian	1 (0.5%)	1 (0.5%)	1 (0.5%)
American Indian or Alaska Native	1 (0.5%)	1 (0.5%)	1 (0.5%)
Other	3 (1.4%)	2 (0.9%)	2 (1%)
Ethnicity n(%)			
Hispanic/Latino	30 (14%)	29 (13.6%)	34 (16.8%)
Not Hispanic/Latino	185 (86%)	184 (86.4%)	168 (83.2%)
Body Mass Index			
Mean (standard deviation)	28.8 (7.2)	27.8 (5.2)	28.0 (6.2)
Median	27.2	26.9	27.1
Min, Max	17.9, 72.3	16.9, 46.8	16.8, 72.3

Source: Reviewer's Table Generated from ADSL Dataset Trial LIN-MD-01

The disposition of patients randomized into Trial LIN-MD-10 is provided in the table below. There were more premature discontinuations from the Linaclotide treatment groups relative to the placebo group (11.2% placebo; 18.8% Linaclotide 145µg; 17.6% Linaclotide 290µg). However, there was not a large discrepancy in the number of discontinuations between the 145µg and 290µg Linaclotide doses. Of the treatment withdrawals, the majority were secondary to adverse events, the most common of which was diarrhea. Early drop-outs due to adverse events appeared to decrease overtime, (which may reflect better tolerance of study drug treatment). Likewise, there were more patients in the Linaclotide arms that either withdrew consent or were lost to follow-up. The majority of the withdrawals due to protocol violations were from patients in the placebo arm but was the percentage was comparable to that of the Linaclotide 145µg arm. Not surprisingly more patients in the placebo arm withdrew to insufficient therapeutic response.

Table 10 Disposition of Study Participants in Trial LIN-MD-01

Reason for Discontinuation	Placebo N=215 n (%)	LIN 145µg N = 213 n (%)	LIN 290µg N = 205 n (%)	Totals
Trial Completers	191 (88.8%)	173 (81.2%)	169 (82.4%)	533 (84.2%)
Premature Withdrawals	24 (11.2%)	40 (18.8%)	36 (17.6%)	100 (15.8%)
Reasons for Withdrawal				
Adverse Event	10 (4.7%)	21 (9.9%)	20 (9.8%)	51 (8.1%)
Insufficient Therapeutic Response	4 (1.9%)	0	1 (0.5%)	5 (0.8%)
Lost to Follow-up	1 (0.5%)	9 (4.2%)	6 (2.9%)	16 (2.5%)
Other Reasons	3 (1.4%)	1 (0.5%)	2 (1.0%)	6 (0.9%)
Protocol Violations	4(1.9%)	3 (1.4%)	1 (0.5%)	8 (1.3%)
Withdrawal of Consent	2 (0.9%)	6 (2.8%)	6 (2.9%)	14 (2.2%)

Source: Reviewer's Table Generated from ADSL Dataset and Modified using Table 10.1-1 Clinical Study Report LIN-MD-01 p. 81.

There were a total of 66 protocol violations meeting criteria for ICH Clinical Report Guidelines for protocol deviations. Of the 66 deviations, 8 involved patients who entered the trial despite not satisfying entry criteria; 5 involved patients receiving the wrong dose of test product; and 46 involved use of a prohibited concomitant medication. Use of a prohibited concomitant medication may affect the efficacy outcome results. However, none of the protocol deviations appeared to affect the efficacy outcomes or safety conclusions.

All efficacy analyses were based on the Intent-to-Treat (ITT) population. A spontaneous bowel movement (SBM) was defined as a bowel movement that occurred in the absence of laxative, enema, or suppository use on either the calendar day of the bowel movement or the calendar day before the bowel movement. A complete spontaneous bowel movement (CSBM) was defined as a SBM that was associated with a sense of complete evacuation.

The primary efficacy assessment used to determine the primary efficacy variable (12-week CSBM overall responder during the 12 weeks of the treatment period), was the IVRS information that determined if a bowel movement was a CSBM. Each day during the treatment period, the patient called the IVRS and provided the number of bowel movements that he or she had since the call on the previous day. (Note: Patients were asked to call at the same time each day.) For each bowel movement, the patient also answered if the bowel movement was associated with a sense of complete evacuation. The patient was also asked if he or she took any rescue medications to treat his or her constipation since the previous day's call. Over the course of the 12-week double-blind treatment period, compliance rates (defined as the proportion of patients with $\geq 80\%$ complete calls) were 72.6% for placebo patients, 75.1% for Linaclotide145µg/day patients, and 75.7% for Linaclotide290-µg/day patients. One might expect a lower rate of compliance in the placebo group if patients were not experiencing the desired outcome and relief of their symptoms.

The original results of the primary efficacy endpoint (12-week CSBM Overall Responder) are provided in the table below. (Note: A 12-week CSBM Overall Responder was a subject 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

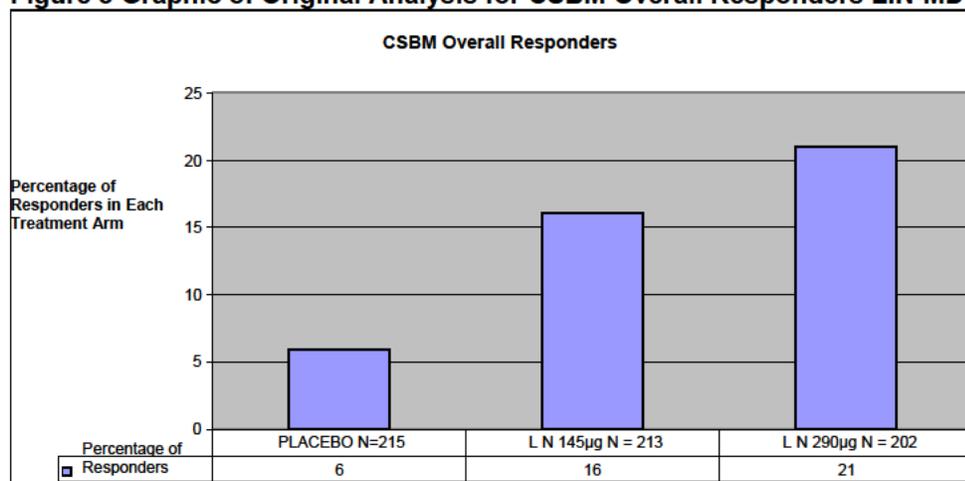
greater and increased by 1 or more from baseline. If a patient did not have CSBM frequency data for a particular week of the treatment period, the patient was not considered a CSBM weekly responder for that week.)

Table 11 Original Analysis of Primary Efficacy Parameter (CSBM Overall Responder) for 12-Week Treatment Period Trial LIN-MD-01 ITT Population

Parameter	PLACEBO N = 215	LIN 145µg N = 213	LIN 290µg N = 202
	n (%)	n (%)	n (%)
Overall CSBM Responder	13 (6%)	34 (16.0%)	43 (21.3%)
Difference In Responder Rate (Linaclotide%– Placebo%)		10	15.3
p-Value by MCP		0.0012	<0.0001

Source: Reviewer's Table with Modifications using Table 11.4.1.1-1 from Clinical Study Report for LIN-MD-01 p.89

Figure 3 Graphic of Original Analysis for CSBM Overall Responders LIN-MD-01



Source: Reviewer's Graphic

According to the applicant, the initial determination of a patient being a 12-week CSBM Overall Responder or CSBM Weekly Responder did not incorporate IVRS call compliance. Therefore a patient that had less than 4 IVRS responses could potentially be treated as a responder. However if a patient prematurely discontinued from the trial and the patient's final treatment week contained less than 4 days of data, the patient was not considered a CSBM Weekly Responder for that week or any of the subsequent missed weeks of the 12 week Treatment Period. Following an information request, the applicant performed a sensitivity analysis of the primary efficacy endpoint where a trial participant with less than 4 complete IVRS calls in a Treatment Period week was considered a nonresponder for that week. The primary endpoint (12 week CSBM overall responder) was then recalculated based on the new "modified" definition of a CSBM Weekly Responder. During each week of the 12 weeks of the treatment period, the proportion of patients who were CSBM weekly responders was greater for each dose of Linaclotide relative to placebo. The results of the 12 week CSBM Overall Responder sensitivity analysis supported the original analysis and showed no appreciable differences in the 12-week CSBM Overall responder rates when patients with less than 4 complete IVRS calls per week were not considered Weekly CSBM responders.

These results were verified by the clinical reviewer. The reader is also referred to the statistical review for additional sensitivity analyses of the primary efficacy endpoint.

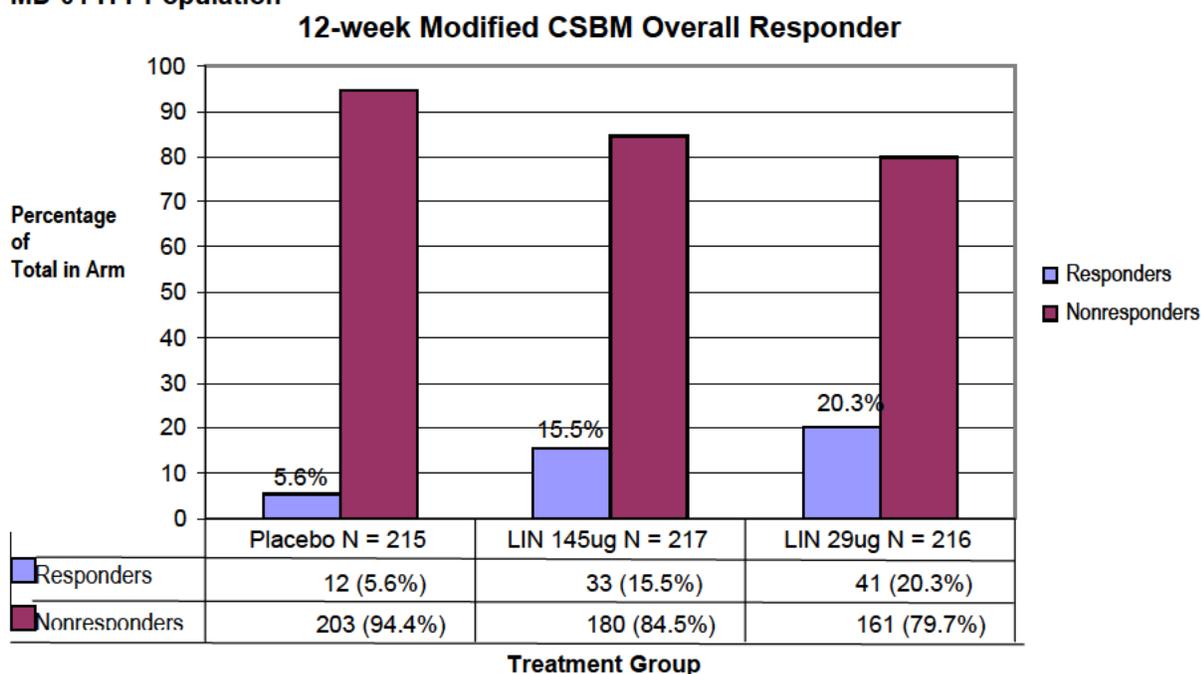
Table 12 Analysis of Modified CSBM Overall Responders for 12-Week Treatment Period Trial LIN-MD-01 ITT Population[±]

Parameter Outcome	PLACEBO N = 215 n (%)	LIN 145µg N = 213 n (%)	LIN 290µg N = 202 n (%)
Responder	12 (5.6%)	33 (15.5%)	41 (20.3%)
Nonresponder	203 (94.4%)	180 (84.5%)	161 (79.7%)
Difference In Responder Rate (Linaclotide%- Placebo%)		9.9	14.7
p-value		0.0011	<.0001

Source: Reviewer's Table Adapted from Table 14.4.1.1C from Response dated January 19, 2012 to Information Request dated December 22, 2011

± For this Modified Table: A 12 week-CSBM overall responder is a patient who is 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, increased by 1 or more from baseline and who completed at least 4 IVRS calls for that week.

Figure 4 Graphic Depiction of Modified CSBM Overall Responder 12 Week Treatment Period Trial LIN-MD-01 ITT Population



Source: Reviewer's Graphic

“Prior studies that investigated medical treatments for chronic idiopathic constipation, have utilized the following primary outcomes: frequency rate of SBM during a specified time frame; proportion of subjects with weekly rescue free bowel movement rate ≥ 3 ; occurrence of a bowel movement within 8 hours following daily administration of study medication; change in average weekly SBM frequency at week 3; and CSBM overall responder defined as a subject who meets the criteria of being a CSBM weekly responder (patient who has a CSBM frequency during the week that is at least 3 CSBMs/week and increases by at least 1 CSBM/week from pretreatment) for 9 out of the 12 weeks.”¹⁶

The aforementioned modified CSBM overall responder is the endpoint that is currently accepted by the Division as a meaningful clinical outcome for trials conducted in patients with chronic idiopathic constipation. The 12 week duration is acceptable for the study of treatments used in chronic conditions. In the opinion of this reviewer, it seems appropriate that the primary efficacy endpoint include an assessment of the effect of treatment on complete spontaneous bowel movements. Constipation has been defined by physicians as three or fewer bowel movements per week.¹⁷ However, while most health care providers define constipation based on stool frequency, patients define constipation as a multi-symptom disorder that includes hard stools, straining, pain when passing a bowel movement and a feel of incomplete evacuation.¹⁰ The primary endpoint used by the applicant appears to incorporate clinical elements from both the patient and physician perspectives.

In a SEALD consult dated May 7, 2008, the endpoint reviewer concluded that the clinical meaningfulness of the CSBM overall responder endpoint was unclear and recommended that the sponsor include a patient rating of change question which quantifies the patient's assessment of improvement. The SEALD consult also stated at that time that the sponsor had not justified that the list of items, proposed as secondary endpoints, represented a complete and comprehensive list of the clinically important symptoms of constipation, based upon patient input. For example, the SEALD reviewer stated that the symptom, abdominal discomfort, appears to be more representative of irritable bowel syndrome, as opposed to chronic idiopathic constipation. In addition, the SEALD reviewer stated that although patient ratings of change (e.g. constipation severity) can be useful in describing a clinically significant change, and supporting primary efficacy assessments, they are not recommended for labeling purposes.

In this application, secondary variables were used to assess "patient rating of change questions". There were 7 key secondary efficacy parameters which measured change from baseline, as recommended by the SEALD reviewer. The symptom severity assessments were very subjective and in the opinion of this reviewer difficult to interpret. For example, during the Pretreatment and Treatment Period daily IVRS calls, patients answered a series of questions about the severity of their abdominal symptoms. Using a 5 point ordinal scale, patients rated their "abdominal pain" "abdominal discomfort" and "bloating" as "None" (1), "Mild" (2), "Moderate" (3), "Severe" (4) or "Very Severe" (5) over the preceding 24 hours. Likewise patients rated the degree of straining as "Not at all = 1"; "A little bit = 2"; "A moderate amount = 3"; "A great deal = 4" or "An extreme amount = 5". The difference in "abdominal pain" and "abdominal" discomfort may not be completely clear and patients were not given instructions on how to differentiate between the two. In addition, for questions such as this, one can not be sure that all respondents have the same understanding of what constitutes each symptom assessed and one is unable to adequately objectively quantify differences between each of the ordinal categories. What one patient may have considered "Severe" (5) may be the equivalent of what another patient considered "Moderate" (3).

Patients were asked to assess treatment satisfaction at pre-specified intervals (e.g. Week 2, Week 4, Week 8) and assess their constipation severity and degree of relief on a weekly basis. For example in a weekly assessment, a patient was asked, "Compared to before you started this study, how would you rate your constipation symptoms during the past 7 days?"

Responses were “1 = Completely relieved”; “2 = Considerably relieved”; “3 = Somewhat relieved”; “4 = Unchanged”; “5 = Somewhat worse”; “6 = Considerably worse”; and “7 = As bad as I can imagine”. Patients were asked to reflect on the state of their condition prior to initiation of the trial. With each progressive week, the level of recall bias may have increased, further making these results less useful for interpretation. According to the applicant, the p value for all key secondary efficacy parameters was statistically significant using the prespecified method of statistical analysis and controlling for multiplicity. Excluding the CSBM and SBM frequency rates, given the subjective nature of the secondary endpoints, this reviewer does not recommend the inclusion of secondary endpoints in the labeling of this product. The reader is referred to the review of the biostatistician for more information. The results of the 7 key secondary efficacy parameters are included in the table below.

Table 13 Overview of Key Secondary Efficacy Parameters for the 12 Week Treatment Period Trial LIN-MD-01 ITT Population

Parameter	Placebo (N = 215)	Linaclotide 145 µg/day (N = 213)			Linaclotide 266 µg/day (N = 202)		
		LS Mean (SE)	LS Mean (SE)	LSMD (95% CI)	p-Value (Significant by MCP)	LS Mean (SE)	LSMD (95% CI)
Changes from baseline							
CSBM weekly frequency rate	0.614 (0.209)	2.011 (0.215)	1.397 (0.89, 1.91)	< 0.0001 (yes)	2.653 (0.217)	2.040 (1.52, 2.56)	< 0.0001 (yes)
SBM weekly frequency rate	1.113 (0.265)	3.446 (0.272)	2.333 (1.69, 2.98)	< 0.0001 (yes)	3.675 (0.275)	2.562 (1.91, 3.22)	< 0.0001 (yes)
Stool consistency	0.572 (0.098)	1.823 (0.100)	1.251 (1.02, 1.49)	< 0.0001 (yes)	2.009 (0.103)	1.437 (1.20, 1.68)	< 0.0001 (yes)
Severity of straining	-0.554 (0.060)	-1.141 (0.061)	-0.587 (-0.73, -0.44)	< 0.0001 (yes)	-1.208 (0.063)	-0.654 (-0.80, -0.51)	< 0.0001 (yes)
Constipation severity	-0.306 (0.062)	-0.908 (0.063)	-0.602 (-0.75, -0.45)	< 0.0001 (yes)	-0.954 (0.064)	-0.648 (-0.80, -0.49)	< 0.0001 (yes)
Abdominal discomfort	-0.271 (0.043)	-0.455 (0.044)	-0.185 (-0.29, -0.08)	0.0006 (yes)	-0.485 (0.045)	-0.215 (-0.32, -0.11)	< 0.0001 (yes)
Bloating	-0.224 (0.048)	-0.432 (0.049)	-0.209 (-0.33, -0.09)	0.0005 (yes)	-0.485 (0.049)	-0.261 (-0.38, -0.14)	< 0.0001 (yes)

Source: Modified from Table T1.4.1.1-1 Applicant's Clinical Study Report for Trial LIN-MD-01 p.89

Note: For secondary efficacy parameters, comparisons with placebo are based on an ANCOVA model with treatment group and geographic region as factors and baseline value as a covariate. ANCOVA = analysis of covariance; CI = confidence interval; CSBM = complete spontaneous bowel movement; ITT = intent to treat; LS = least squares; LSMD = least squares mean difference (relative to placebo); MCP = multiple comparison procedure; N = population size; SBM = spontaneous bowel movement

The applicant performed subgroup analyses of the primary and secondary efficacy endpoints. The subgroups included gender, age, race, and geographic region. Efficacy was maintained and consistent across these subgroup analyses. The reader is referred to the statistical

review for details. In addition, the applicant also assessed 14 additional efficacy parameters. Again the reader is referred to the statistical review for details.

During the trial, patients were allowed to use center–dispensed, protocol-defined laxatives (5 mg bisacodyl tablets or 10 mg bisacodyl suppositories) as rescue medication if ≥ 72 hours had passed since the previous bowel movement or when the patient’s symptoms became intolerable. Usage of rescue medication, or any other laxative, suppositories, or enemas during the treatment period in each of the Linaclotide dose groups was compared to usage in the placebo group. The following endpoints for rescue medications were assessed and compared for each of the treatment arms:

- The proportion of patients who reported using per-protocol rescue medications or any other laxative, suppository, or enema
- The change from baseline in the percentage of patient reported days of using rescue medications or any other laxative, suppository or enema
- The proportion of patients who had an increase from baseline in the percentage of days where per-protocol rescue medication or any other laxative, suppository, or enema were used, as reported by patients during the treatment period. (Note: The day of randomization was excluded from the calculation of baseline percentages because the use of rescue medications would make a patient ineligible for randomization at the beginning of the trial.)

Patients in the Linaclotide treatment groups used less rescue medications. Of the placebo patients, 74.9% used rescue medication during the 12-week treatment period compared with 58.2% of patients in the Linaclotide 145µg arm and 51.5% of patients in the Linaclotide 290µg arm. A summary of the per-protocol rescue medication use during the 12-week treatment period in the ITT population is presented in the table below reproduced from the applicant’s submission.

Table 14 Summary of Rescue Medication Use During 12 Week Treatment Period - Trial LIN-MD-01 ITT Population

	Placebo (N = 215)	Linaclotide	
		145 µg (N = 213)	290 µg (N = 202)
Patients using Rescue Medication, n (%)	161 (74.9)	124 (58.2)	104 (51.5)
Difference (Linaclotide– placebo)	—	-16.7	-23.4
Patients with an increase in number of days of rescue medication use, n (%)	63 (29.3)	36 (16.9)	32 (15.8)
Difference (Linaclotide– placebo)	—	-12.4	-13.5
Change from baseline in percentage of days of rescue medication use			
LSMC from baseline (SE)	-3.122 (1.267)	-5.800 (1.299)	-5.805 (1.312)

Source: Reviewer’s table modified from Table 11.4.1.4.3-1 Clinical Study Report LIN-MD-01

LSMC=Least squared mean change

Of the 633 patients enrolled in the study, 370 (58.5%) experienced at least 1 adverse event (AE). There were a total of 890 adverse events. The following tables provide an overview of the number of patients experiencing adverse events and the adverse events that occurred in the safety population for Trial LIN-MD-01. There was 1 additional death and 1 additional serious adverse event (SAE) not included in the applicant's AE summary table in the clinical study report. One patient (#0570150) experienced two SAEs. Additional information on these patients is provided in the following text.

Table 15 Overview of Patients Experiencing Adverse Events During Treatment Period Trial LIN-MD-01 Safety Population

	Placebo N=215	LIN 145µg N = 213	LIN 290µg N = 205
	n (%)	n (%)	n (%)
Total Number of Patients Experiencing an AE by Treatment Arm (TEAE)	116 (53%)	139 (65%)	116 (57%)
Number of Patients Experiencing at least 1 Treatment RELATED Adverse Event [±]	33 (15.3%)	68 (31.9%)	50 (24.3%)
Number of Patients Experiencing Each Category of Adverse Events			
Death	0	1 (0.5%)	1 (0.5%)
Serious Adverse Event (SAE)	4 (1.9%)	3 (1.4%)	7 (3.4%)
AE Resulting in Early Withdrawal	10 (4.7%)	21 (9.9%)	20 (9.8%)

Source: Reviewer's Table

[±] Treatment Related AEs includes those AEs whose relationship to treatment was assessed by the Investigator as "Definite, Probable, or Possible"

Table 16 Overview of Adverse Events During Treatment Period Trial LIN-MD-01 Safety Population

	Placebo	LIN 145µg	LIN 290µg
	n (%)	n	n
Number of Treatment Emergent Adverse Events By Treatment Arm	277	333	280
Category of Adverse Event			
Death	0	1 (0.3%)	1 (0.5%)
Serious Adverse Event	4 (1.4%)	3 (0.9%)	9 (3.2%)
Adverse events leading to discontinuation from trial	12 (4.3%)	32 (9.6%)	28 (10%)
Adverse events leading to interruption of trial treatment	11 (4%)	16 (4.8%)	20 (7.1%)

Source: Reviewer's Table generated from Applicant's ADAE dataset Trial LIN-MD-01

Table 17 Overview of Treatment Emergent Adverse Event Severity Trial LIN-MD-01 Safety Population

Number of Treatment Emergent Adverse Events By Treatment Arm	Placebo N = 277	LIN 145µg N = 333	LIN 290µg N = 280
AE Severity	n (%)	n (%)	n (%)
Mild	156 (56.3%)	162 (48.6%)	124 (44.3%)
Moderate	105 (37.9%)	157 (47.1%)	128 (45.7%)
Severe	16 (5.8%)	14 (4.2%)	27 (9.6%)
Unclassified	0	0	1 (0.4%)

Source: Reviewers Table generated from LIN-MD-01 ADAE dataset.

ICH E2A defines an adverse event as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Likewise adverse drug reactions are all noxious and unintended responses to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. The applicant defined a treatment emergent adverse event as an adverse event that was not present before the date of the first dose of double-blind study drug for the treatment period, or if the adverse event was present before the date of the first dose of double-blind study drug for the treatment period, the adverse event increased in severity during the specified treatment period.

Overall, more patients in both of the Linaclotide groups experienced adverse events when compared to the placebo group. Patients in the Linaclotide groups also experienced more treatment emergent adverse events than those in the placebo group. Patients in the 145µg Linaclotide group experienced more treatment emergent adverse events (TEAEs) than patients in the other two treatment arms. However, a larger percentage of patients in the 290µg Linaclotide group (3.4%) experienced serious adverse events (SAEs) relative to the other treatment arms (1.9% placebo, 1.4% Linaclotide 145µg). Per protocol, an SAE was an AE that:

- Resulted in death

- Was an immediate threat to life
- Required hospitalization, or prolongation of existing hospitalization
- Resulted in persistent or significant disability/incapacity
- Was a congenital abnormality or birth defect

In addition to the above, important medical events that did not result in death, were not life-threatening, or did not require hospitalization were considered SAEs when, based upon appropriate medical judgment, they were considered to have jeopardized the patient and may have required medical or surgical intervention to prevent one of the outcomes listed above.

The percentage of adverse events leading to temporary interruption of drug treatment was higher in the 290µg Linaclotide group relative to the other treatment groups (7.1% vs. 4% placebo and 4.7% 145µg Linaclotide group). Most of the adverse events reported were mild to moderate in severity. There was a higher percentage of severe adverse events in the 290µg Linaclotide arm (9.6%) relative to the placebo (5.8%) and Linaclotide 145µg (4.2%) arms. (Note: For an adverse event to be considered “severe,” the AE caused the patient to experience severe discomfort or severely limited or prevented the patient’s normal activities and represented a definite hazard to health. Additionally, prescription drug therapy and/or hospitalization may have been employed to treat the AE.) The percentage of adverse events leading to early treatment withdrawal was comparable between the two Linaclotide groups (9.6% in the Linaclotide 145µg arm vs. 10% in the Linaclotide 290µg arm) and both Linaclotide groups led to a higher percentage of withdrawals than placebo. There were no substantial differences in treatment duration among the treatment groups. The mean duration of treatment was 79.1 days for placebo patients, 75.4 days for the Linaclotide 145µg group, and 76.0 days for Linaclotide 290µg group.

The most common adverse events experienced by patients in Trial LIN-MD-01 were diarrhea, flatulence, and abdominal pain. Diarrhea was the most common related treatment emergent adverse event. The mean time (\pm SD) from the first dose of double-blind treatment to the first TEAE of diarrhea was 14.6 ± 19.7 days for the Linaclotide treated patients compared with 29.8 ± 24.0 days for the placebo treated patients. The most frequently reported treatment emergent adverse events that occurred at an incidence of at least 3% and at an incidence greater than placebo are presented in the table below reproduced from the applicant’s submission. There did not appear to be a relationship between Linaclotide dose and incidence of treatment emergent adverse events.

Table 18 Treatment Emergent Adverse Events Experienced in > 3.0% of Either Linaclotide Treatment Groups and at an Incidence Greater than Placebo Trial LIN-MD-01 Safety Population

	Placebo N=215	LIN 145µg N = 213	LIN 290µg N = 205
	n (%)	n (%)	n (%)
Total Number of Patients Experiencing an AE by Treatment Arm (TEAE)	116 (53%)	139 (65%)	116 (57%)
Preferred Term Adverse Events			
Diarrhea	6 (2.8%)	42 (19.7%)	30 (14.6%)
Flatulence	13 (6.0%)	16 (7.5%)	13 (6.3%)
Upper respiratory tract infection	14 (6.5%)	16 (7.5%)	9 (4.4%)
Abdominal pain	5 (2.3)	11 (5.2%)	11 (5.4%)
Nausea	7 (3.3%)	8 (3.8%)	9 (4.4%)
Abdominal distention	7 (3.3%)	7(3.3%)	8 (3.9%)
Urinary tract infection	8 (3.7%)	8 (3.8%)	6 (2.9%)
Sinusitis	5 (2.3%)	8 (3.8%)	4 (2.0%)
Nasopharyngitis	7 (3.3%)	3 (1.4%)	8 (3.9%)

Source: Reviewer's Table Generated from ADAE dataset LIN-MD-01 with Modifications from Table 12.2.2-1 Trial LIN-MD-01 Clinical Study Report page 125.

There were two deaths during the conduct of this trial. Neither of the deaths was assessed as being related to study treatment. Patient #0090105 was a 66 year old white female in the Linaclotide 290µg treatment arm, whose death was secondary to pancreatic cancer 2.5 months after her last dose of study drug. The investigator assessed this event as unrelated to study drug. Patient #0160101 was a 49 year old white female. Patient 0160101 was also enrolled as IBS-C patient 281002 in Trial MCP-103-202. This patient died 2 days after her last dose of Linaclotide 145µg as a result of a self-inflicted fentanyl overdose.

A total of 10 Linaclotide treated patients and 4 placebo treated patients experienced at least 1 Serious Adverse event. Two patients (#0570150 and #0050101) experienced two SAEs. The majority of the SAEs occurred in the 290µg Linaclotide arm. A summary describing patients that experienced a Serious Adverse Event is presented in the table below. Only 1 patient (#0140103) experienced an SAE that was assessed as possibly related to study drug.

Table 19 Descriptive Summaries of Serious Adverse Events Trial LIN-MD-01 Safety Population

Subject Number	Treatment Arm	Exact/Reported Term for SAE	MedDRA preferred Term for SAE	Number of Days to SAE Start	Narrative	AE Severity	Investigator Assessment of Relatedness
0050101	Linaclotide 290µg	Lymphoma Dehydration	Lymphoma Dehydration	68	68 year old African-American female with chronic idiopathic constipation and past medical history of hypertension, hypercholesterolemia, coronary artery disease, heartburn, hemorrhoids, type I diabetes, and medication allergies. Several concomitant medications. On Day 48 of Linaclotide treatment patient experienced painful swelling in right submandibular area, which was treated with antibiotics and steroids. Nine days later, physical exam significant for firm tender mass in right submandibular region. CT with and without contrast revealed a cystic mass, submandibular nodes measuring up to 1.5cm and degenerative cervical spine changes. Fine needle aspiration of the mass revealed a malignant lymphoma, consistent with non-Hodgkin's lymphoma. A full body PET scan revealed abnormal metabolic activity consistent with neoplasm in multiple areas. The patient was admitted to hospital for a suprahyoid neck dissection. The patient was able to complete the Linaclotide trial. At the time of database lock, the SAE was ongoing. There was no narrative to describe the SAE of dehydration. However, this SAE appeared in the dataset for the study.	Moderate Moderate	Unrelated Unrelated
0090105 (DEATH)	Linaclotide 290µg	Pancreatic Cancer	Pancreatic Carcinoma	8	66 year old White nonsmoking female with chronic idiopathic constipation and past medical history that included environmental allergies, partial left ear deafness, chronic bronchitis, asthma, peptic ulcer disease, nonmalignant bladder tumor, hyperlipidemia, esophageal diverticulum, hypertension, gastroesophageal reflux disease, peripheral neuropathy, anxiety, and depression. Concomitant medications included atorvastatin (subsequently replaced by lovastatin), duloxetine, and lisinopril. Prior to study entry the patient complained of abdominal discomfort, intermittent alternating diarrhea and constipation and weight loss. An EGD and colonoscopy revealed gastric polyps, small hiatal hernia, normal colon and hemorrhoids. Patient began study drug treatment on January 8, 2009. On Day 8 of treatment, the patient was diagnosed with extensive ascites and treated for pain with acetaminophen/propoxyphene. A CT scan of the abdomen and pelvis showed enlargement of the pancreatic duct with subtle focus of decreased attenuation at the head of the pancreas, suspicious for pancreatic carcinoma. The body and tail of the pancreas was also atrophic. 2.5 liters of cloudy ascites were removed during an ultra-sound guided abdominal paracentesis. Cytology of the	Severe	Unrelated

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Subject Number	Treatment Arm	Exact/Reported Term for SAE	MedDRA preferred Term for SAE	Number of Days to SAE Start	Narrative	AE Severity	Investigator Assessment of Relatedness
					ascitic fluid showed no malignant cells. The serum:ascites albumin gradient was high. Patients severe abdominal pain persisted and required treatment with protocol prohibited concomitant medications. On January 30, 2009, study drug was discontinued and the patient was withdrawn from the trial. On (b) (6) patient was again hospitalized for ascites. Initial workup included an abdominal MRI and large volume paracentesis. On (b) (6), patient underwent exploratory laproscopy and biopsy of peritoneal nodules were positive for grade 2 adenocarcinoma. Patient was diagnosed with metastatic pancreatic adenocarcinoma. The patient began chemotherapy on an undisclosed date and died on (b) (6) (approximately (b) (6) later).		
0090109	Placebo	Cellulitis of Left Shoulder	Cellulitis	47	43 year old White female with chronic idiopathic constipation and a history of adhesive capsulitis of the left shoulder, seasonal allergies, labyrinthitis, asthma, bronchitis, recurrent pneumonia, tuberculosis, pertussis, gastric ulcer, hyperlipidemia, peripheral edema, benign uterine cysts/tumors, constricted bladder, migraine headaches, type II diabetes, depression, insomnia, generalized osteoarthritis, and sinusitis. Multiple concomitant medications. On 2/19/2009, patient visited an orthopedic surgeon for left shoulder pain which began 1 year prior and progressively worsened over time. Patient also complained of pain with motion, weakness, numbness, tingling, and swelling of shoulder. Physical exam was positive for tenderness over the greater tuberosity and posterior joint line. Following imaging studies, the patient was diagnosed with left shoulder adhesive capsulitis. On (b) (6), the patient had left shoulder diagnostic arthroscopy and manipulation with arthroscopic capsulotomy. She was treated with hydrocodone/acetaminophen for pain and discharged home. 5 days later the patient presented with increased left shoulder pain and increased warmth over the region. Physical exam was significant for slight redness over the anterior and lateral shoulder region that extended onto her anterior chest wall. The patient was afebrile with a normal white blood cell count and sedimentation rate. She was admitted to the hospital and treated with IV antibiotics and pain medication. The wound was open to air with steristrips. The patient responded well to treatment and was discharged home on oral antibiotics and pain medication. The patient was able to complete the Linaclotide trial and the cellulitis resolved without sequelae.	Severe	Unrelated
0100102	Placebo	Cardiac Chest Pain	Angina pectoris	7	66-year-old White woman with chronic constipation, and a history of gastroesophageal reflux disease (GERD), dyspepsia, asthma, seasonal allergies, sinus headaches, chronic sinusitis, positive Helicobacter pylori (H. pylori), colonic diverticulosis, hyperlipidemia, osteoarthritis, osteopenia, type II diabetes, anxiety,	Severe	Unrelated

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Subject Number	Treatment Arm	Exact/Reported Term for SAE	MedDRA preferred Term for SAE	Number of Days to SAE Start	Narrative	AE Severity	Investigator Assessment of Relatedness
					smoking and fatigue. Multiple concomitant medications. No prior history of cardiac disease. On (b) (6), (Day 7 of study drug treatment) patient was admitted to the hospital after she presented with "shooting" left-sided chest pain that radiated from the neck into the shoulder and down the arm to the hand. All laboratory tests including cardiac enzymes were normal. Patient also had a normal cardiac stress test. Chest xray was significant for hypoinflated lungs with bibasilar atelectasis and an enlarge cardiac silhouette. Urinalysis was positive for white cell. Culture of the urine grew E.Coli sensitive to Levaquin. The patient was treated with Levaquin for the UTI and Nexium for GERD. Patient was discharged on Hospital (b) (6) with a diagnosis of chest pain, urinary tract infection, asthma, and GERD. The chest pain was thought to be secondary to GERD. Patient was able to complete the Linaclotide trial.		
0140103 (Drop out)	Linaclotide 145µg	Bronchitis	Bronchitis	85	66 year old White female with chronic idiopathic constipation and a past medical history of insomnia, hypercholesterolemia, rheumatoid arthritis, and situational depression. Concomitant medications included methotrexate, diphenhydramine, and folic acid. Patient was traveling when she developed cough and fatigue. She presented to the emergency room with complaints of continuous, unrelenting cough that kept her awake at night and poor oral intake. Patient was orthostatic in the ER. She was admitted to the hospital on (b) (6) for bronchitis and poor oral intake with orthostatic hypotension. Physical exam was significant for decreased breath sounds and bibasilar rales posteriorly. Chest Xray was negative. The patient was treated with IV fluids and study drug was discontinued. A chest CT with and without contrast on (b) (6), revealed an indeterminate 12X7mm density in the right lower lobe and no evidence of pulmonary embolus. The patient improved and was discharged on hospital (b) (6) on azithromycin 250 mg daily, benzonatate 100 mg every 6 hours, and budesonide/formoterol (160/4.5) as needed for cough. The event resolved without sequelae. On April 8, the principal investigator prescribed ondansetron for nausea prophylaxis, and the patient received single injections of cefotaxime, ceftriaxone, dexamethasone and betamethasone. The patient decided to withdraw from the study for personal reasons.	Severe	Possible
0160101 (DEATH)	Linaclotide 145µg	Acute Fentanyl Toxicity	Drug Toxicity	52	49 year old White female with chronic idiopathic constipation and past medical history of neck and back pain. Past medical history was also significant for schizophrenia and bipolar disorder which, per report, was not reported to the test site. The patient was not receiving treatment for her mental conditions. Urine drug screen was negative prior to the patient beginning study drug treatment. During	Severe	Unlikely

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Subject Number	Treatment Arm	Exact/Reported Term for SAE	MedDRA preferred Term for SAE	Number of Days to SAE Start	Narrative	AE Severity	Investigator Assessment of Relatedness
					the 4 weeks of study drug treatment, the patient did not report any adverse events. She was able to complete Visit 5 of the trial. The patients family reported that she saw a physician on January 21, 2009 and was prescribed esomeprazole which she did not fill. On (b) (6), the patient was found deceased at her home. Numerous medication bottles were present in her home, including those labeled to contain oxycodone + acetaminophen, morphine, lorazepam, and diazepam. Four 50 µg fentanyl patches were present on the patient's upper arms. An autopsy was performed. Significant findings included a left adrenal neoplasm, a well circumscribed chronic inflammatory nodule on the left lower lobe of the lung, and swelling in the right lower extremity. Levels of fentanyl in the patient's blood and liver were consistent with the number of patches found on the patients body. Final autopsy diagnoses were acute fentanyl toxicity and adrenal cortical adenoma. The immediate cause of death was fentanyl overdose. According to the narrative, none of the medications detected in the patient's body (bupropion, citalopram, fentanyl, hydrocodone, and diphenhydramine) were reported to the study coordinator.		
0380105	Placebo	Nonworsening Multinodular Goiter	Goitre	63	71 year old White female with past medical history significant for chronic constipation, multinodular goiter, osteoporosis, hypertension, high cholesterol, gastroesophageal reflux disease (GERD), intermittent peripheral edema, allergic conjunctivitis, vitamin B12 deficiency, and dysphagia. Concomitant medications included risedronate sodium, acetylsalicylic acid, atenolol, simvastatin, ezetimibe, esomeprazole, furosemide, olopatadine hydrochloride, and Vitamin B12. Physical examination on Day 1 was significant for a goiter. Patient reported that the multinodular goiter had been present for 17 years, but no work-up was done. Patient was referred to an endocrinologist. A thyroid panel on March 10, 2009 was normal. Findings on a thyroid scan performed on (b) (6) were consistent with multinodular goiter. The consulting physician recommended a thyroid lobectomy because of the patients difficulty swallowing. On (b) (6), the patient was hospitalized and underwent left thyroid lobectomy, isthmusectomy, and exploration/visualization of the recurrent laryngeal nerve and parathyroid glands. Histology revealed that the thyroid mass was benign. Study drug was temporarily held from May 28, 2009 to May 29, 2009. Patient was discharged from the hospital on (b) (6). The patient was able to complete the trial	Severe	Unrelated
0430104	Placebo	Cholelithiasis	Cholelithiasis	39	50 year old White female chronic constipation, and a history of GERD, depression, rheumatoid arthritis, seasonal allergies, hypothyroidism, hypercholesterolemia,	Severe	Unrelated

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					and obesity. Concomitant medications included prednisone, duloxetine, iron, calcium, levothyroxine, fexofenadine HCl/pseudoephedrine HCl, estradiol, Vitamin C, esomeprazole, gabapentin, acetylsalicylic acid, multivitamin, lovastatin, folic acid, venlafaxine hydrochloride, and methotrexate. Following the start of double-blind treatment the patient experienced episodes of post-prandial bloating and intermittent abdominal pain. On (b) (6) after starting study drug treatment), the patient presented to the ER with post-prandial epigastric pain radiating to the back, bloating, and nausea. Patient also reported shortness of breath with food intake but otherwise review of systems was negative. Physical exam significant for a soft abdomen with mild tenderness in the epigastric region. CBC, chemistry, electrolytes, and ECG were normal. Patient was admitted. Because of an elevated D-dimer level on admission she underwent a CT angiogram of the chest, abdomen and pelvis. CT findings were suggestive of an inflammatory process of the gallbladder. Abdominal ultrasound was significant for a fatty liver, stone in the gallbladder and normal size common bile duct. Patient was diagnosed with acute cholecystitis. On (b) (6) she had elective laproscopic cholecystectomy. The patient was continued study medication and was able to complete the study.		
0450108	Linaclotide 290µg	Diverticulitis	Diverticulitis	64	57 year old African American female with past medical history of chronic constipation, diverticulosis, hypertension, seasonal allergies, and insomnia. Concomitant medications (b) (6) included amlodipine, fluticasone, and diphenhydramine. On (b) (6) of study drug treatment), the patient awoke at 4AM with severe abdominal pain in the left lower quadrant. She presented to the ER and was admitted to the hospital. Physical exam was significant for marked tenderness in the left lower quadrant with guarding and questionable rebound tenderness. Plain films of the abdomen was normal. Abdominal and pelvic CT with contrast showed acute diverticulitis of the distal descending colon, no abscess or free air, and a suspected hydrosalpinx of the left fallopian tube. White blood cell count was elevated with lower than expected lymphocytes. Patient was started on levofloxacin and Flagyl. On hospital (b) (6) the patient had recovered and discharged home on oral levofloxacin and metronidazole and advised to eat a low residue diet. (Note study drug was held for 3 days from March 21 to March 23, 2009). On March 24, 2009, the patient restarted study drug and was able to complete the trial. The SAE resolved on April 7, 2009.	Severe	Unrelated
0450117 (Drop Out)	Linaclotide 290µg	Cholecystitis	Cholecystitis	18	45 year old White male with chronic constipation. No concomitant medications. On Day 14 of study drug treatment, patient complained of bloating and abdominal	Severe	Unrelated

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					discomfort for which he was given simethicone drops to use as needed. The following day, March 31, 2009, the patient was seen for his scheduled study visit and prescribed ranitidine for probable gastritis. Patient did not improve. On (b) (6) patient presented to the ER. The ranitidine was discontinued. Labs were significant for elevated liver enzymes. Patient was admitted and diagnosed with gallstones. A hepatobiliary scan showed no evidence of cystic duct or common bile duct obstruction. Right upper quadrant ultrasound showed a gallbladder full on stones. There was a positive sonographic Murphy's sign suggesting acute cholecystitis. On (b) (6), a laparoscopic cholecystectomy was performed. Surgical pathology report included chronic cholecystitis, cholelithiasis, and a benign cystic duct lymph node. The patient's condition improved. Liver enzymes decreased. Patient was discharged on (b) (6) with oxycodone/acetaminophen and ranitidine. The patient discontinued from the study as a result of this event.		
0570150	Linaclotide 290µg	Dehydration Orthostatic Hypotension	Dehydration Orthostatic Hypotension	57	34 year old White female with history of chronic constipation, anorexia, and hypercholesterolemia. Concomitant medication included (Cilest) (b) (6) ethnylestradiol/norgestimate for birth control. On treatment (b) (6) patient presented to the clinic complaining of nausea and one episode of diarrhea. The patient felt faint, dizzy, and weak on arrival and was found to be hypotensive and hypoglycemic on physical exam. Patient was orthostatic. Urinalysis showed elevated ketones and protein. The dehydration was thought to be secondary to the nausea, vomiting and diarrhea. The patient was rehydrated over 3 hours and able to tolerate a granola bar. She later vomited in clinic. The patient was transferred to the ER but was not hospitalized. She recovered in the ER and was prescribed Bactrim twice a day at discharge. Discharge diagnoses were bladder and food poisoning vs. viral gastroenteritis. However, per patient report she did not take the Bactrim and an infection was never confirmed. The patient underwent outpatient bilateral breast augmentation surgery on (b) (6). Study drug treatment was temporarily stopped for 7 days and resumed on May 28, 2009. The patient was able to complete the study.	Moderate Moderate	Unlikely Unlikely
0690108 (Drop Out)	Linaclotide 145µg	Partial Small Bowel Obstruction	Small intestinal Obstruction	8	45 year old African-American female with chronic idiopathic constipation and past medical history of overactive bladder, cystocele, depression, insomnia, tension headaches, osteoporosis, recurrent back pain, rectocele, and multiple drug allergies. The patient was s/p hysterectomy in 2003 with subsequent vaginal wound dehiscence that required reduction. Concomitant medications included quetiapine and risedronate. Patient was treated with study drug from December	Severe	Unrelated

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Subject Number	Treatment Arm	Exact/Reported Term for SAE	MedDRA preferred Term for SAE	Number of Days to SAE Start	Narrative	AE Severity	Investigator Assessment of Relatedness
					22, 2008 until December 28, 2008. On (b) (6), she suddenly developed abdominal pain without nausea, vomiting or diarrhea. She presented to the ER and admitted to the hospital the same day. Approximately 3 hours after admission, the patient developed diffuse moderate suprapubic tenderness and abdominal distension. She was treated with IV meperidine, ondansetron, and hydromorphone hydrochloride. A CT scan showed free fluid and possible evidence of an ischemic loop of small intestines versus enteritis. White count was elevated. Surgeon noted rebound tenderness in right lower quadrant and positive Rovsing's sign. The following day the patient had an exploratory laparotomy which revealed an incarcerated internal hernia fixed to the anterior abdominal wall involving the omentum and a trapped loop of small bowel as well as dense anterior abdominal wall adhesions. The hernia was reduced and the adhesions were lysed. Pre and postoperative diagnoses were acute surgical abdomen, closed loop bowel obstruction, internal hernia, and intestinal adhesions. On (b) (6) the patient was discharged with hydrocodone/acetaminophen for pain. The (b) (6) the patient returned to the ER with increasing pain which was treated with IV hydromorphone hydrochloride and ondansetron. The patient was discharged from the study. She was reportedly well on January 12, 2009		
0820105 (Drop-Out)	Linaclotide 290µg	Infection left ring finger s/p glomus tumor excision	Postoperative Wound Infection	47	47 year old white female with past medical history of chronic constipation, dyspepsia, hemorrhoids, invert T-waves on ECT, recurring headaches, depression, ovarian cysts and eczema. Patient was s/p hysterectomy (1993). Concomitant medications included Lac-lotion, venlafaxine, and an estradiol patch for hormone replacement therapy. In November of 2008, patient injured her finger while working. She developed swelling, tenderness, and a blue mark on her fingernail. Shortly thereafter the patient was diagnosed with a glomus tumor of the left 4 th finger. On (b) (6), a biopsy of the digit nail was suggestive of glomangioma and showed no malignancy. The glomus tumor was removed on an outpatient basis and the patient discharged with oral Keflex. 5 days later the patient returned to clinic complaining of increased swelling, pain and erythema over 24 hours. The antibiotic was changed to ciprofloxacin. On (b) (6) the patient was admitted for treatment with IV antibiotics. Xray of the digit was unremarkable. The patient's finger did not improve. Tissue culture from the finger grew pseudomonas. Patient was discharged with a diagnosis of cellulitis and scheduled for operative intervention as an outpatient. Included hydrocodone/acetaminophen as needed for pain. Bacitracin, Augmentin, and Ciprofloxacin. Patient was readmitted on (b) (6) for recurrent infection of	Severe	Unrelated

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Subject Number	Treatment Arm	Exact/Reported Term for SAE	MedDRA preferred Term for SAE	Number of Days to SAE Start	Narrative	AE Severity	Investigator Assessment of Relatedness
					the nail. Tissue cultures were again positive for pseudomonas. Nail and bone biopsies showed benign soft tissue with chronic inflammation and granulation. A second incision and drainage was performed. On March 10, 2009 the patient took her last dose of study drug. On (b) (6), she was discharged home on IV vancomycin, gentamicin, and ciprofloxacin through a PICC line. By March 27, the patient began to improve. At the time she was being treated with ciprofloxacin for osteomyelitis. On (b) (6), the swelling of the finger had completely resolved. There was no evidence of infection. The patient was discharged with full function and mobility of her finger. Per report the patient was discontinued from the trial for noncompliance.		
0880129 (Drop-Out)	Linaclotide 290µg	Recurrent Endometriosis	Endometriosis	28	38 year old White female. Past medical history of chronic constipation, anxiety, migraines, endometriosis, drug hypersensitivity, genital herpes, and contact dermatitis. Concomitant medications included citalopram hydrobromide, topiramate, drospirenone w/ethinylestradiol, and rizatriptan benzoate. Patient's endometriosis had previously been treated laparoscopically (most recent procedure 2006). At screening she did not have signs or symptoms related to her endometriosis. Later it became apparent that the patient really had several months of worsening pelvic pain. On March 4, 2009 (Day 28 of treatment), her OB-GYN noted recurrent endometriosis during a routine visit. On (b) (6) the patient had a total hysterectomy and left salpingo-oophorectomy. Surgical pathology report revealed chronic cervicitis, weakly proliferative endometrium, focal endometriosis, and paratubal cysts. On (b) (6) patient was discharged. The patient was discontinued from trial	Severe	Unrelated

Source: Reviewer's Table

The incidence of adverse events leading to discontinuation is presented by preferred term for each of the treatment groups in the table below. There were more patients in the Linaclotide treatment groups who experienced an adverse event resulting in an early withdrawal (4.7% placebo, 9.9% Linaclotide 145µg, 9.8% Linaclotide 290µg). There did not appear to be substantial differences in the percentage of patients who withdrew because of an Adverse Event in the 145µg Linaclotide group vs. the 290ug Linaclotide group. The most common adverse event leading to early withdrawal was diarrhea (5.6% Linaclotide 145ug, 4.9% Linaclotide 290µg) and abdominal pain (1.9% Linaclotide 145µg, 1.0% Linaclotide 290µg). Overall, there was no obvious relationship between the dose of Linaclotide and the type of AEs leading to discontinuation from the trial..

Table 20 Percentage of Patients Withdrawing from Trial due to Adverse Event Trial LIN-MD-01 Safety Population

	Placebo N=215	LIN 145µg N = 213	LIN 290µg N = 205
	n (%)	n (%)	n (%)
Number of Patients Experiencing Adverse Events Resulting in Early Withdrawal	10 (4.7%)	21 (9.9%)	20 (9.8%)
Number of Patients Experiencing each AE by Preferred term			
Diarrhea	1 (0.5%)	12 (5.6%)	10 (4.9%)
Abdominal pain	1 (0.5%)	4 (1.9%)	2 (1.0%)
Nausea	2 (0.9%)	2 (0.9%)	1 (0.5)
Headache	3 (1.4%)	0	2 (0.5%)
Defecation urgency	0	1 (0.5%)	2 (1.0%)
Dehydration	0	0	2 (1.0%)
Fecal incontinence	0	1 (0.5%)	1 (0.5%)
Flatulence	1 (0.5%)	1 (0.5%)	0
Vomiting	1 (0.5%)	1 (0.5%)	0
Abdominal distension	0	1 (0.5%)	0
Abdominal pain upper	0	1 (0.5%)	0
Cholecystitis	0	0	1 (0.5%)
Decreased appetite	0	1 (0.5%)	0
Small intestinal obstruction	0	1 (0.5%)	0
Dyspepsia	0	1 (0.5%)	0

Source: Reviewer's Table generated from ADAE dataset from Trial LIN-MD-01 with modification from Clinical Study Report LIN-MD-01 Table 12.3.1-1 p.126

Descriptive statistics were used to describe the changes from baseline in physical exam findings, vital signs, and laboratory values. Overall there were no clinically meaningful differences between the placebo and two Linaclotide groups for any of the laboratory parameters, or physical exam findings. This is not surprising, given that the drug has low systemic availability. The following tables reproduced from the applicant's submission, summarize the changes from baseline in electrolytes and vital signs. .

Table 21 Changes from Baseline in Electrolytes Trial LIN-MD-01 Safety Population

Parameter	Placebo (N = 215)		Linaclotide			
			145 µg/day (N = 213)		290 µg/day (N = 205)	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Calcium, mmol/L						
Baseline	214	2.43 ± 0.11	210	2.42 ± 0.11	201	2.42 ± 0.11
End of study	214	2.41 ± 0.11	210	2.42 ± 0.10	201	2.41 ± 0.11
Change	214	-0.02 ± 0.11	210	-0.01 ± 0.12	201	-0.01 ± 0.11
Chloride, mmol/L						
Baseline	214	103.0 ± 2.5	210	103.2 ± 2.4	201	103.7 ± 2.8
End of study	214	103.4 ± 2.7	210	103.6 ± 2.5	201	103.8 ± 2.6
Change	214	0.4 ± 2.5	210	0.4 ± 2.5	201	0.0 ± 2.4
Magnesium, mmol/L						
Baseline	214	1.75 ± 0.14	210	1.73 ± 0.14	201	1.75 ± 0.15
End of study	214	1.76 ± 0.14	210	1.74 ± 0.13	201	1.75 ± 0.14
Change	214	0.01 ± 0.13	210	0.01 ± 0.13	201	-0.01 ± 0.13
Phosphorus, mmol/L						
Baseline	214	1.16 ± 0.16	210	1.18 ± 0.15	201	1.16 ± 0.20
End of study	214	1.15 ± 0.17	210	1.19 ± 0.18	201	1.17 ± 0.17
Change	214	-0.01 ± 0.18	210	0.02 ± 0.18	201	0.00 ± 0.22
Potassium (mmol/L)						
Baseline	214	4.30 ± 0.43	210	4.33 ± 0.48	201	4.33 ± 0.47
End of study	214	4.26 ± 0.40	210	4.31 ± 0.48	201	4.28 ± 0.41
Change	214	-0.04 ± 0.38	210	-0.02 ± 0.44	201	-0.04 ± 0.39
Sodium, mmol/L						
Baseline	214	139.5 ± 2.1	210	139.7 ± 2.7	201	140.0 ± 2.3
End of study	214	139.7 ± 2.1	210	140.0 ± 2.5	201	140.0 ± 2.2
Change	214	0.3 ± 2.3	210	0.4 ± 2.4	201	0.0 ± 2.0

Source: Table 12.4.2.1-1 Clinical Study Report LIN-MD-01 p. 130

Table 22 Changes from Baseline Vital Signs Trial LIN-MD-01 Safety Population

Parameter	Placebo (N = 215)		Linaclotide			
			145 µg/day (N = 213)		290 µg/day (N = 205)	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Systolic blood pressure, mm Hg						
Baseline	214	118.7 ± 14.3	212	118.8 ± 15.4	202	117.7 ± 14.4
End of study	214	117.7 ± 15.2	212	117.7 ± 15.5	202	116.0 ± 14.1
Change	214	-1.1 ± 12.8	212	-1.1 ± 12.8	202	-1.7 ± 12.6
Diastolic blood pressure, mm Hg						
Baseline	214	73.6 ± 9.1	212	75.1 ± 9.2	202	74.2 ± 9.2
End of study	214	74.3 ± 9.0	212	73.9 ± 9.0	202	72.9 ± 9.4
Change	214	0.7 ± 8.3	212	-1.2 ± 7.8	202	-1.2 ± 8.5
Pulse rate, beats per minute						
Baseline	214	71.4 ± 8.8	212	70.9 ± 10.4	202	72.3 ± 10.1
End of study	214	71.3 ± 10.0	212	70.1 ± 10.5	202	70.6 ± 10.0
Change	214	-0.1 ± 8.6	212	-0.9 ± 9.3	202	-1.6 ± 9.8
Body weight, kg						
Baseline	214	77.3 ± 19.4	212	75.1 ± 15.5	202	74.2 ± 15.9
End of study	214	77.5 ± 19.7	212	74.9 ± 15.5	202	73.8 ± 15.6
Change	214	0.2 ± 2.0	212	-0.1 ± 2.2	202	-0.4 ± 2.2

Source: Table 12.5.1-1 Clinical Study Report LIN-MD-01 p. 134

One would expect that if patients taking Linaclotide experienced more dehydration relative to the placebo groups, there would have been a greater increase (not decrease) in pulse rates for these two groups relative to placebo. One might have also anticipated larger drops in body weight, SBP, and DBP. These findings were not observed.

The number of patients experiencing potentially clinically significant changes in laboratory values is presented in the table below. Only changes in the absolute lymphocyte count and absolute neutrophil count were remarkable. Stimulation of guanylate cyclase-c receptors by uroguanylin agonists increases the intracellular production of cGMP signaling a cascade that results in down-regulation of inflammatory cytokines. The observed changes in absolute neutrophil count and absolute lymphocyte count may reflect the anti-inflammatory potential of this product.¹⁸

Table 23 Number of Patients with Potentially Clinically Significant Laboratory Parameters During the Double-Blind Treatment Period Trial LIN-MD-01 Safety Population

Laboratory Parameter	PCS Criteria	Placebo N = 215 n/N1 (%)	Linaclotide	
			145 µg/day N = 213 n/N1 (%)	290 µg/day N = 205 n/N1(%)
Hematology				
Hematocrit	< 0.9 × LLN	0/214	0/210	1/200 (0.5)
Hemoglobin	< 0.9 × LLN	3/213 (1.4)	1/210 (0.5)	3/200 (1.5)
Absolute lymphocyte cell count	> 1.5 × ULN	0/212	1/209 (0.5)	0/196
	< 0.8 × LLN	1/212 (0.5)	4/209 (1.9)	7/196 (3.6)
Absolute neutrophil cell count	> 1.5 × ULN	0/210	2/208 (1.0)	4/200 (2.0)
	< 0.8 × LLN	3/210 (1.4)	5/208 (2.4)	6/200 (3.0)
Platelet count	> 1.5 × ULN	0/214	1/209 (0.5)	0/200
	< 0.5 × LLN	0/214	1/209 (0.5)	0/200
Red blood cell count	> 1.1 × ULN	0/214	0/210	1/200 (0.5)
	< 0.9 × LLN	0/214	0/210	1/200 (0.5)
White blood cell count	> 1.5 × ULN	0/213	1/210 (0.5)	0/201
Chemistry				
Alanine aminotransferase	≥ 3 × ULN	0/214	0/210	1/201 (0.5)
Albumin	> 1.1 × ULN	0/214	1/210 (0.5)	0/200
Aspartate aminotransferase	≥ 3 × ULN	1/214 (0.5)	0/210	1/201 (0.5)
Bicarbonate	< 0.9 × LLN	1/214 (0.5)	0/210	1/201 (0.5)
Bilirubin, total	> 1.5 × ULN	1/214 (0.5)	0/208	0/201
Blood urea nitrogen	> 1.2 × ULN	3/214 (1.4)	0/209	2/200 (1.0)
Calcium	> 1.1 × ULN	1/214 (0.5)	0/209	0/201
Cholesterol	> 1.6 × ULN	1/213 (0.5)	1/206 (0.5)	0/199
Creatinine	> 1.3 × ULN	1/213 (0.5)	1/210 (0.5)	1/200 (0.5)

Source: Table 12.4 2.2-1 Clinical Study Report LIN-MD-01 page 137 PCS = Potentially clinically significant

N = Number of patients randomized to that treatment arm.

N1 = Number of patients with available non-baseline value and at least 1 post baseline assessment

n = Number of Patients (of the N1 patients) who met PCS criteria at least once during the Treatment

ULN = Upper Limit of Normal LLN = Lower limit of Normal

Single ECGs were performed at screening and upon trial completion. Additionally a subset of study participants had triplicate ECGs performed at all scheduled study visits (except for Visit 4). For those patients with triplicate ECGs, only the average of the 3 consecutive ECG values for each of ECG parameter was used to generate summary statistics. There were four abnormal ECG findings reported as TEAEs during the treatment period (2 in the placebo group and 1 in each of the Linaclotide groups). Only 1 patient (placebo patient #0880132) had a clinically significant ECG at the end of the trial. This patient had first degree atrioventricular block. With the exception of the R-R interval, overall there were no clinically meaningful changes in ECG parameters. The R-R interval is an assessment of ventricular rate. A negative change (i.e. shortening of the R-R interval) indicates a increase of the heart

rate. Patients in the placebo group had a mean change from baseline of -1.5 ± 109.4 (SD). Patients in the Linaclotide 145 μ g group had a mean change from baseline of -6.5 ± 111.4 (SD). Patients in the Linaclotide 290 μ g group had a mean change from baseline of -13.4 ± 101.9 . The large standard deviations associated with each value are indicative of a wide range of heart rate values. Therapeutic agents that target the guanylate cyclase c receptors have been proposed for use in the treatment of salt dependent forms of hypertension.¹⁹ Drugs that lower blood pressure may have a rebound effect of increasing the heart rate depending on the mechanism of action. Likewise, if Linaclotide were associated with diarrhea and resultant hypotension, one would have expected to see an increase in heart rates. Given the limited systemic availability of the drug, this finding is not overly concerning but it is quite interesting..

5.3.3 Clinical Overview of Results Trial MCP-103-303

The reader is referred to Section 6 of this review for additional integrated information. Trial MCP-103-303 (hereafter also referred to as MCP-303) was multi-center Randomized, Double-Blind, Placebo-Controlled, Parallel-group, Phase 3 Trial assessing the safety and efficacy of two doses of Linaclotide (145 μ g and 290 μ g) over a 12-week treatment period. The initial treatment period was followed by a 4 week Randomized-Withdrawal (RW) period. The data from the trial demonstrated that both the 145 μ g and 290 μ g doses of Linaclotide resulted in a statistically significant improvement (over placebo) in the primary efficacy variable, 12-week Complete Spontaneous Bowel Movement (CSBM) Overall Responder. Interestingly, the treatment effect of the 290 μ g dose over placebo was numerically less than the treatment effect of the 145 μ g dose over placebo. (The CSBM overall responder rates were placebo 3.3%, Linaclotide 145 μ g 20.3%, and Linaclotide 290 μ g 19.0% using the modified 12 week CSBM overall responder definition.) It appears that the 290 μ g Linaclotide dose does not offer any additional efficacy than the 145 μ g Linaclotide dose. However, the trial was not designed to compare the superiority or noninferiority of one Linaclotide dose over the other.

Statistically significant changes were also demonstrated in the secondary efficacy parameters which included CSBM frequency rate; spontaneous bowel movement (SBM) frequency Rate; stool consistency; straining; constipation severity; abdominal discomfort; and bloating. For most parameters, improvements over placebo were observed within the first week of treatment with both doses of Linaclotide. The treatment effects were sustained over the 12-weeks of the treatment period.

During the Randomized-Withdrawal (RW) period, patients were re-randomized to one of the five treatment sequences below:

- 290 μ g Linaclotide → 290 μ g Linaclotide (290 μ g Linaclotide administered in the Treatment period followed by 290 μ g Linaclotide administered in the RW period)
- 290 μ g Linaclotide → placebo (290 μ g Linaclotide administered in the Treatment period followed by placebo in the RW period)
- 145 μ g Linaclotide → 145 μ g Linaclotide (145 μ g Linaclotide administered in the Treatment period followed by 145 μ g Linaclotide administered in the RW period)
- 145 μ g Linaclotide → placebo (145 μ g Linaclotide administered in the Treatment period followed by placebo administered in the RW period)

- Placebo → 290µg Linaclotide(Placebo administered in the Treatment period followed by 290µg Linaclotide administered in the RW period)

The purpose of the RW period was to demonstrate the durability of response to drug treatment. The RW period was also used to determine if a rebound (i.e. a worsening of symptoms at baseline) or other withdrawal effects occurred after Linaclotide treatment was withdrawn. During the RW period, the CSBM rates for Linaclotide-treated patients re-randomized to placebo decreased to rates similar to those seen in placebo-treated patients at week 12 of the Treatment Period. CSBM rates for Linaclotide treated patients who continued on the same study drug treatment during the RW period were maintained. CSBM rates in patients treated during the Treatment Period with placebo and then re-randomized to 290µg Linaclotide during the RW period increased to levels of patients in the original 290µg Linaclotide dose group at week 12 of the Treatment Period.

Overall there were no additional safety signals identified during the review of this trial. Diarrhea was again the most common treatment emergent adverse event (TEAE) reported in patients taking Linaclotide during both the Treatment Period and RW Period. In the Treatment Period, diarrhea was reported in 6.7% of placebo patients; 12.4% of patients taking Linaclotide 145µg, and 13.8% of patients taking Linaclotide 290µg. Diarrhea was also the most common reason for early withdrawal in Linaclotide-treated patients. Rates of discontinuation due to diarrhea were 3.2% in the Linaclotide 145µg arm, 2.8% in the Linaclotide 290µg arm, and 0.5% in the placebo arm. The incidence of SAEs was comparable in Linaclotide-treated and placebo-treated patients. There were no clinically meaningful trends in changes from baseline for vital signs, laboratory assessments, and ECGs parameters across the treatment arms. With the exception of the group of patients that were re-randomized to Linaclotide 290µg during the RW period following initial treatment with placebo, the severity and incidence of TEAEs observed were similar between the treatments of the RW sequences. The incidence and category of adverse events observed in patients re-randomized to Linaclotide 290µg following placebo treatment were consistent with that observed in patients taking Linaclotide 290 µg during the first 4 weeks of the Treatment period. There was no rebound worsening of constipation observed in patients re-randomized to placebo following treatment with either the 145µg or the 290µg doses of Linaclotide.

Changes in analytical procedures resulted in changes in the dose-strength expression for the proposed drug product. The dose strengths of 150µg and 300µg used in the protocols and statistical analysis plans are analogous to the 133µg and 266µg doses used in the clinical study report. These doses correspond to the final 145µg and 290µg Linaclotide doses proposed by the applicant for use as the commercial product. The 145µg and 290µg Linaclotide doses reflect the total Linaclotide content. Throughout the review of this trial the 145µg and 290µg Linaclotide doses are used. (The reader is referred to Section 6.1.8 of this review.) In addition, when necessary, Linaclotide is also referred to by the abbreviation LIN or the proposed tradename LINZESS.

According to the applicant, 2 patients enrolled in Trial MCP-303 had previously participated in or were actively participating in another trial of Linaclotide at the time of their enrollment. This was a violation of the protocol. The applicant developed rules for inclusion of the data from

duplicate patients in the efficacy and safety analyses. These rules are outlined in Section 7.1 of this review. The reader is also referred to the statistical review of Dr. Milton Fan. Duplicate patients are listed in the table below.

Table 24 Duplicate Patients in Trial MCP-103-303

MCP-103-303 Patient ID Number	Duplicate Patient ID Number (Second Study ID)	Treatment Groups (Treatment Period/RW Period)	Description of Deviation
0123004	0240105 (LIN-MD-01) (LIN-MD-02)	Placebo/Linaclotide290µg	Patient enrolled under another ID number in another Phase 3 Linaclotide trial and a long-term safety trial of Linaclotide. Upon completion of LIN-MD-01, the patient enrolled in the open-label long-term safety trial LIN-MD-02 (patient ID 0240105 for both trials) While still participating in the long-term trial, the patient enrolled in trial MCP-103-303. The patient was concurrently enrolled in both the long-term and Phase 3 trial for approximately 4 months
0423004	011019 (MCP-103-201)	Linaclotide290µg/Placebo	Patient was enrolled under another ID number in a Phase 2b Linaclotide trial. Patient previously completed the Phase 2b study MCP-103-201 (placebo arm). Subsequently the patient enrolled and completed the Phase 3 trial MCP-103-303.

A detailed description of the Trial Periods and analysis weeks is presented in the Table below reproduced from the Applicant's submission.

Table 25 Description of Evaluation Periods for Analysis Trial MCP-103-303

Period	Analysis Week	Begins	Ends
Pretreatment (Baseline)	Week -2	Days -14	Day -8
	Week -1	Day -7	Day 1 (time of randomization)
Treatment Period	Week 1	Day 1 (time of randomization)	Day 7
	Week 2	Day 8	Day 14
	Week 3	Day 15	Day 21
	Week 4	Day 22	Day 28
	Week 5	Day 29	Day 35
	Week 6	Day 36	Day 42
	Week 7	Day 43	Day 49
	Week 8	Day 50	Day 56
	Week 9	Day 57	Day 63
	Week 10	Day 64	Day 70
	Week 11	Day 71	Day 77
	Week 12	Day 78	Day of last Treatment Period Dose (usually Day 84)
Randomized Withdrawal Period	Week 1	RW Day 1	RW Day 7
	Week 2	RW Day 8	RW Day 14
	Week 3	RW Day 15	RW Day 21
	Week 4	RW Day 22	Day of Last RW Period Treatment dose (usually Day 28)

For this review, data and analyses from the Treatment Phase of Trial MCP-103-303 are presented first in Section 5.3.3.1 followed by data and analyses from the Randomized-Withdrawal (RW) phase in Section 5.3.3.2

5.3.3.1 Results from Treatment Phase of Trial MCP-103-303

There were 1147 patients screened to enter the trial. Approximately 18% of those screened were screening failures. Another 26% of those screened were pre-treatment failures. These large numbers may impact the generalizability of trial outcomes to the larger U.S. population. A total of 103 trial centers enrolled 643 patients (209 Placebo patients; 217 Linaclotide 145µg patients; 217 Linaclotide 290µg patients). Patient populations and disposition are presented by treatment group in the Table below.

Table 26 Patient Populations and Enrollment Trial 12 Week Treatment Period MCP-103-303

Patients Screened = 1147				
Screen Failures = 205				
Pretreatment Failures = 299				
	Placebo	Linaclotide		Total
		145µg	290µg	
Patients Randomized	209	217	217	643
Safety Population	209	217	217	643
Intent-to-Treat Population	209	217	216	642
12 Week Study Completers	177	186	177	540
Patients Re-randomized at Week 12	177	186	177	540
16 Week Trial Completers	175	183	175	533

Source: Reviewer's Table Generated from ADSL dataset with Modifications from Tables 14.1.1 and 14.1.3A Clinical Study Report Trial

MCP-103-303 pages 192 - 202.

Note: Treatment arms presented in this table are the actual Treatment Arms to which patients were randomized at the beginning of the first treatment period.

Per protocol the populations were defined as follows:

- Screened Population: All patients who had a Screening Visit and were assigned a patient ID number (PID)
- Randomized Population: All patient in the Screening Population who were randomized to a treatment group at the Randomization Visit
- Safety Population: All patients in the Randomized Population who received ≥ 1 dose of double-blind study drug during the Treatment Period
- Intent-to-Treat(ITT): Patients in the Safety Population who also had ≥ 1 post-randomization entry of the primary efficacy assessment (i.e. the daily interactive voice response system {IVRS} information that determined whether an SBM was a CSBM)

For the purpose of this review, all analyses were performed using the ITT population. All trial enrollees were included in the Safety population. Ninety-nine percent (99%) were included in the Intent-to-Treat population. Almost 84% (83.9% or 540 patients) of the 643 patients enrolled in the trial completed the 12 week Treatment Period per protocol requirements and were re-randomized into the 4 week Randomized-Withdrawal (RW) period. Almost 83% (82.8%) of the 643 enrollees completed all 16 weeks of the trial (i.e. both Treatment and RW periods). The Linaclotide 290µg group had the highest percentage of early withdrawals (19.4%). Both of the other treatment groups had approximately 16% early withdrawals.

The majority of people enrolled were Caucasian (75%), Non-Hispanic (95%), and female (87%). Baseline demographics across treatment groups were comparable. In each of the treatment arms approximately 87-88% of patients were less than 65 years old. Increased aged is associated with chronic constipation. Therefore the trial population may not completely reflect the real world population. The mean age in the placebo group was slightly higher when compared with the other two treatment groups. This was because the placebo group enrolled a higher percentage of patients over the age of 65 years (13.4%) and a smaller percentage of patients < 40 years (24.9%). There was also a higher percentage of Non-Caucasians (27.3%) enrolled in the Linaclotide 290µg group and a smaller percentage of Non-Hispanics in the placebo group (2.9%). However, these small differences in baseline demographics seem unlikely to affect trial outcomes. Baseline characteristics were otherwise equally distributed across treatment arms. Demographic data are presented in the table below.

Table 27 Baseline Demographics of ITT Population Trial MCP-103-303

Characteristic	TRIAL MCP-103-303		
	PLACEBO N = 209	LINACLOTIDE 145µg N = 217	LINACLOTIDE 290µg N = 216
Age (years):			
Mean (standard deviation)	49.3 (14.3)	47.1 (14.2)	47.6 (14.2)
Median	49	47	48
Min, Max	18,85	19,82	18,83
Age Group (years) n(%)			
18 < 40:	52 (24.9%)	67 (30.9%)	65 (30.1%)
40 < 65:	129 (61.7%)	123 (56.7%)	124 (57.4%)
≥ 65:	28 (13.4%)	27 (12.4%)	27 (12.5%)
Sex n(%)			
Male	27 (12.9%)	26 (12%)	28 (13%)
Female	182 (87.1%)	191(88%)	188 (87%)
Race n(%)			
White (Caucasian)	160 (76.6%)	164 (75.6%)	157 (72.7%)
Black	46 (22.0%)	46 (21.2%)	52 (24.1%)
Asian	2 (1.0%)	2 (0.9%)	3(1.4%)
American Indian or Alaska Native	0	1 (0.5%)	0
Other	1 (0.5%)	4 (1.8%)	4 (1.9%)
Ethnicity n(%)			
Hispanic/Latino	6 (2.9%)	13 (6.0%)	15 (6.9%)
Not Hispanic/Latino	203 (97.1%)	204 (94.%)	201 (93.1%)
Body Mass Index			
Mean (standard deviation)	27.8 (5.4)	27.9 (6.5)	28.0 (5.3)
Median	27.6	26.9	27.4
Min, Max	18.1, 50.4	15.1, 69.9	19, 48.6

Source: Reviewer's Table Generated from ADSL Dataset Trial MCP103-303 and verified with Table 14.2.2 of the Clinical Study Report for Trial MCP-103-303.

The percentage of patients who reported an abnormality in any system organ class (SOC) at baseline was comparable across the treatment groups (98.6% placebo; 97.2% Linaclotide 145µg group; 99.1% Linaclotide 290µg group. Patients in the placebo group reported the highest percentage of cardiac disorders, 15.3%, compared with 9.7% in the Linaclotide 145µg group and 12% in the Linaclotide 290µg group. The percentage of patients reporting baseline gastrointestinal disorders was 66.5% in the placebo arm, 65.4% in the Linaclotide 145µg arm, and 73.3% in the Linaclotide 290µg arm. The most commonly reported disorder across all groups was hemorrhoids (34.9% placebo; 33.6% Linaclotide 145µg arm; 39.2% Linaclotide 290µg arm). This would be consistent with a patient population suffering from chronic idiopathic constipation. Interestingly, over a third of patients in all treatment arms suffered from immune system disorders at baseline (36.8% placebo; 40.1% Linaclotide 145µg; 35% Linaclotide 290µg arm). The most commonly reported issues were seasonal allergy and drug hypersensitivity. Over a third of patients in all the treatment arms suffered from metabolic disorders; musculoskeletal and connective tissue disorders; nervous system disorders; and psychiatric disorders (mostly depression). Seventy-six percent (76%) of patients had a prior history of surgical and medical procedures. Nearly 90% of patients in each treatment arm reported concomitant medication use (91.4% placebo arm; 90.8% Linaclotide 145µg arm; 89.4% Linaclotide 290µg arm). Apart from the proton pump inhibitors, the most frequently reported medications were vitamins and drugs used to treat pain; hypercholesterolemia; and clotting prophylaxis.

It seems logical that more patients withdrew due to insufficient therapeutic response from the placebo arm. More patients in both of the Linaclotide arms withdrew consent when compared with the placebo arm. The Linaclotide 290µg arm had the highest percentage of early withdrawals (19%) relative to the other two treatment arms (16.3% Placebo and 15.7% Linaclotide 145µg). The Linaclotide 290µg group also had the highest percentage of protocol violations. The large percentage of patients in the Linaclotide 290µg group who were lost to follow-up (4.6%) relative to the other treatment arms (1.4% placebo and 2.3% Linaclotide 145µg) is a bit concerning, especially when one considers the higher percentage of protocol violations. This may also reflect the lower efficacy results in this dosage group.

A total of 14 patients had protocol violations. Twelve patients violated the requirements for the inclusion/exclusion criteria. During the conduct of the trial, 2 patients were administered the wrong dose. Patient #0273002 was randomized to Linaclotide 145µg but at Visit 6, was dispensed Linaclotide 290µg due to human error in dispensing the wrong kit. The patient remained on the incorrect dose from March 27, 2009, through April 23, 2009, after which she was re-randomized to Linaclotide 145µg in the RW Period and resumed treatment with the lower dose. Patient #0393006 received the incorrect study drug during the RW Period (145µg Linaclotide instead of placebo). Both patients were analyzed as initially randomized. A total of 113 patients took a pre-specified prohibited medication. The disposition of patients in the ITT population of Trial MCP-103-303 is provided in the table below.

Table 28 Disposition (Reasons for Early Withdrawal) Trial MCP-103-303 ITT Population

	Placebo N=209 n (%)	LIN 145µg N = 217 n (%)	LIN 290µg N = 216 n (%)	Totals N = 642 N (%)
12 Week Treatment Period Completers	177 (84.7%)	186 (85.7%)	177 (81.9%)	540 (84.1%)
Overall 16 week Trial Completers	175 (83.7%)	183 (84.3%)	175 (81%)	533 (83%)
Premature Withdrawals	34 (16.3%)	34 (15.7%)	41 (19%)	109 (17%)
Reasons for Withdrawal				
Adverse Event	9 (4.3%)	11 (5.1%)	10 (4.6%)	30 (4.7%)
Insufficient Therapeutic Response	8 (3.8%)	1 (<1%)	2 (<1%)	11 (1.7%)
Lost to Follow-up	3 (1.4%)	5 (2.3%)	10 (4.6%)	18 (2.8%)
Other Reasons	2 (< 1%)	2 (<1%)	0	4 (<1%)
Protocol Violations	4 (1.9%)	3 (1.4%)	7 (3.2%)	14 (2.2%)
Withdrawal of Consent	8 (3.8%)	12 (5.5%)	12 (5.6%)	32 (5.0%)

Source: Reviewer's Table Generated from ADSL Dataset for MCP 103-303

Each day during the treatment period, the patient called the interactive voice response system (IVRS) and provided the number of bowel movements that he or she had since the call on the previous day. (Note: patients were asked to call at the same time each day.) For each bowel movement, the patient also answered if the bowel movement was associated with a sense of complete evacuation. The patient was also asked if he or she took any rescue medications to treat his or her constipation since the previous day's call. Overall, the percentage of patients who were ≥ 80% IVRS compliant during the 12-week Treatment Period was 84% for placebo, 80% for Linaclotide 145µg, and 78% for Linaclotide 290µg. Treatment compliance was calculated as:

$$\frac{(\text{Total number of capsules taken}) \times 100}{(\text{Total number of capsules expected to be taken})}$$

Overall, treatment compliance during the Treatment Period was 96.7% for placebo, 96.5% for Linaclotide 145 µg and 96.9% for Linaclotide 290 µg. The compliance rate remained steady and above the 96% for all groups throughout the 12 weeks of the Treatment Period.

The primary efficacy variable 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. Per protocol, a complete spontaneous bowel movement (CSBM) was defined as a spontaneous bowel movement (SBM) that was associated with a sense of complete evacuation. A SBM was defined as a bowel movement that occurred in the absence of laxative, enema, or suppository use on either the calendar day of the bowel movement or the calendar day before the bowel movement.

"Prior studies that investigated medical treatments for chronic idiopathic constipation, have utilized the following primary outcomes: frequency rate of SBM during a specified time frame; proportion of subjects with weekly rescue free bowel movement rate ≥ 3; occurrence of a bowel movement within 8 hours following daily administration of study medication; change in average weekly SBM frequency at week 3; and CSBM overall responder defined as a subject

who meets the criteria of being a CSBM weekly responder (patient who has a CSBM frequency during the week that is at least 3 CSBMs/week and increase by at least 1 CSBM/week from pretreatment) for 9 out of the 12 weeks.”²⁰ The clinical meaningfulness of the “12-week CSBM Overall Responder” endpoint utilized in this trial was unclear to previous endpoint reviewers. The study endpoints and labeling team has recommended that applicants seeking to develop products for chronic idiopathic constipation also include a patient rating of change question which quantifies the patient’s assessment of improvement.

According to the applicant, the initial determination of a patient being a 12-week CSBM Overall Responder or CSBM Weekly Responder did not incorporate IVRS call compliance. Therefore a patient that had less than 4 IVRS responses in a week could potentially be treated as a responder for the week. Following a solicited information request, the applicant performed a sensitivity analysis of the primary efficacy endpoint where a study participant with less than 4 complete IVRS calls in a Treatment Period week was considered a nonresponder for that week. The “modified” primary endpoint (“12 week CSBM Overall Responder”) was then recalculated based on the new “modified CSBM Weekly Responder” endpoint. The modified weekly and overall CSBM responder endpoints are the endpoints that are currently accepted by the Division as a meaningful clinical outcome for trials conducted in patients with chronic idiopathic constipation.

The 12 week duration is acceptable for the study of treatments used in chronic conditions. It seems appropriate that the primary efficacy assessment measure the effect of treatment on complete spontaneous bowel movements. While most health care providers define constipation based on stool frequency, patients define constipation as a multi-symptom disorder that includes hard stools, straining, pain when passing a bowel movement and a feel of incomplete evacuation.”¹⁰ The primary endpoint used by the applicant incorporates clinical elements from both the patient and physician perspective.

There were 2 tests of the primary efficacy variable (one test comparing each Linaclotide dose to placebo) and 14 tests of the secondary efficacy variables (comparing each Linaclotide dose to placebo for the 7 secondary efficacy variables).

The original analysis of the primary efficacy variable “12 week CSBM Overall responder” for the ITT population is provided in the table below followed by a graphic depiction of the results.

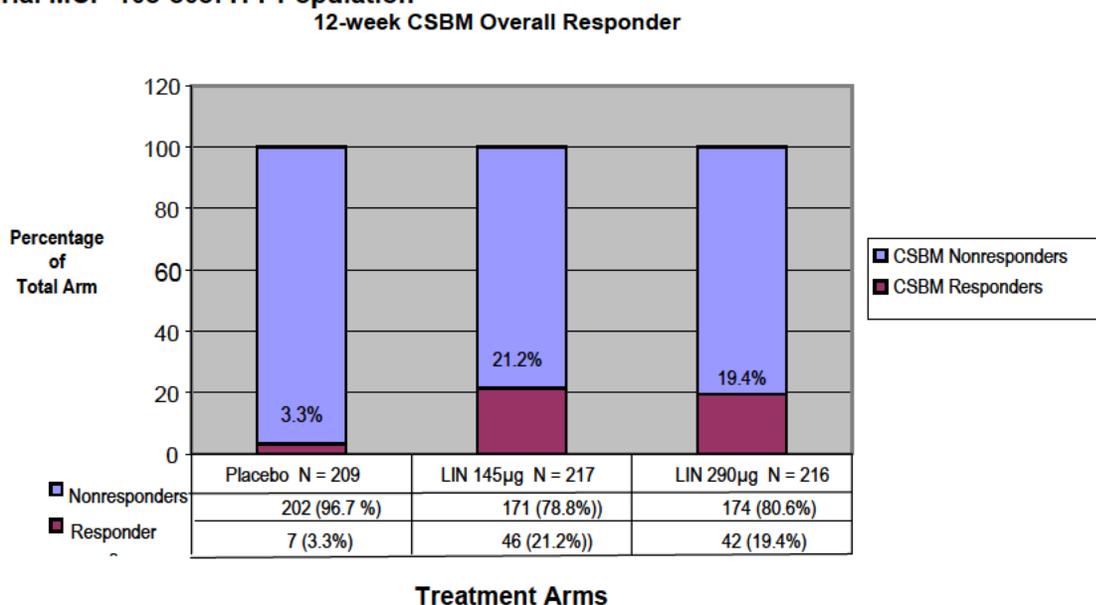
Table 29 Original Analysis of Primary Efficacy Parameter (CSBM Overall Responders) during 12 Week Treatment Period Trial MCP 103-303 ITT Population

Parameter	PLACEBO N = 209	Linaclotide 145µg N = 217	Linaclotide 290µg N = 216
	n (%)	n (%)	n (%)
Overall CSBM Responder	7 (3.3%)	46 (21.2%)	42 (19.4%)
p-Value		<0.0001	<0.0001

Source: Reviewer’s table produced using the ADEFF dataset submitted by the Applicant on August 9, 2011. Confirms Applicant’s Table 14.4.1.1 page 384 Clinical Study Report for MCP-103-303. (p-values reproduced from Applicant’s table were confirmed by the statistical reviewer and presented as reported from the planned analysis after applying pre-specified serial gatekeeping multiple comparisons procedure.) A 12 week CSBM Overall Responder is a patient who was a CSBM Weekly responder for 9 of

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. This analysis did not take into account IVRS call compliance.

**Figure 5 Graphic Depiction of CSBM Overall Responders during 12 week Treatment Period
 Trial MCP-103-303: ITT Population**



There were more patients in each of the Linacotide groups who were overall CSBM responders. The number and percentage of patients who were 12-week CSBM Overall Responders in the Linacotide 145µg arm (46 patients, 21.2%) and Linacotide 290µg arm (42 patients, 19.4%) were numerically greater when compared to placebo (7 patients, 3.3%). These results were also statistically significant. Interestingly the treatment effect of the 290µg dose over placebo was less than the treatment effect of the 145µg dose over placebo. It appears that the 290µg Linacotide dose does not offer any additional efficacy response than the 145µg Linacotide dose. However, the trial was not designed to compare the superiority (or noninferiority) of one Linacotide dose over the other.

As previously stated, the initial determination of a patient being a 12-week CSBM Overall Responder or CSBM Weekly Responder did not incorporate IVRS call compliance. Included in the modified definition was a requirement that a patient have at least 4 IVRS calls for that week to be considered a Weekly Responder. A sensitivity analysis of the primary endpoint was performed using the modified definition of a CSBM responder. The results were statistically significant and depicted in the table and graphic below.

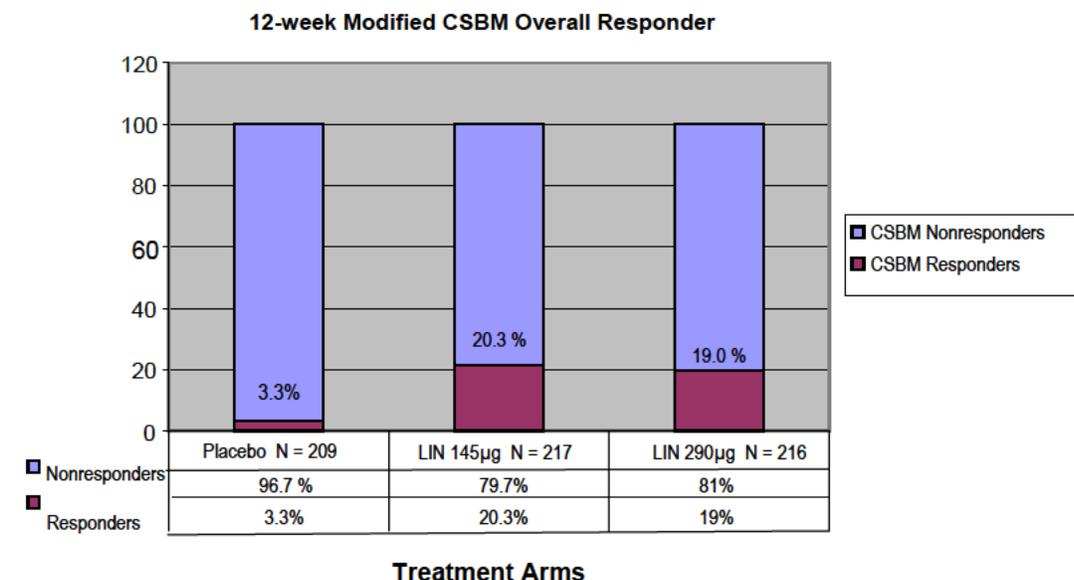
**Table 30 Analysis of Modified CSBM Overall Responders during 12-Week Treatment Period
 Trial MCP-103-303 ITT Population**

Parameter Outcome	PLACEBO N = 209 n (%)	LIN 145µg N = 217 n (%)	LIN 290µg N = 216 n (%)
Responder (Modified) ±	7 (3.3%)	44 (20.3%)	41 (19.0%)
Nonresponder	202 (96.7%)	173 (79.7%)	175 (81.0%)
Difference In Responder Rate (Linaclotide%– Placebo%)		17.0	15.7
p-value		<0.0001	<.0001

Source: Reviewer's Table Generated from Applicant's ADEFF dataset submitted February 8, 2011. Confirms Applicant's Table 14.4.1C Submitted on January 19, 2012 in response to information request sent December 22, 2011. p-values confirmed by the Statistical Reviewer.

± For this Modified Table: A 12 week-CSBM overall responder is a patient who is 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, increased by 1 or more from baseline and who completed at least 4 IVRS calls for that week

**Figure 6 Graphic Depiction of Modified CSBM Overall Responders during 12 Week Treatment Period:
 Trial MCP 103-303 ITT Population**



Source: Reviewer's Graphic Depiction of the Trial Results.

Subgroup analyses of the primary and secondary efficacy endpoints by gender, age, race, and geographic region revealed that efficacy was fairly consistent among the subgroups. The reader is referred to the statistical review for details.

There were seven pre-specified key secondary efficacy variables (measuring change from baseline) assessed by the applicant. As stated previously, in the opinion of this reviewer, excluding the CSMB and SBM frequency rate, the results of the secondary efficacy variables appear to be less quantifiable and are subject to interpretation. Consequently the secondary assessments do not appear to provide useful information (b) (4)

For the sake of completeness, the applicant's assessments of the "secondary efficacy variables" are provided in the table below. According to the applicant the p-values for

all “secondary efficacy parameters” were statistically significant using the prespecified method for statistical analysis. The reader is referred to the review of the biostatistician for more information.

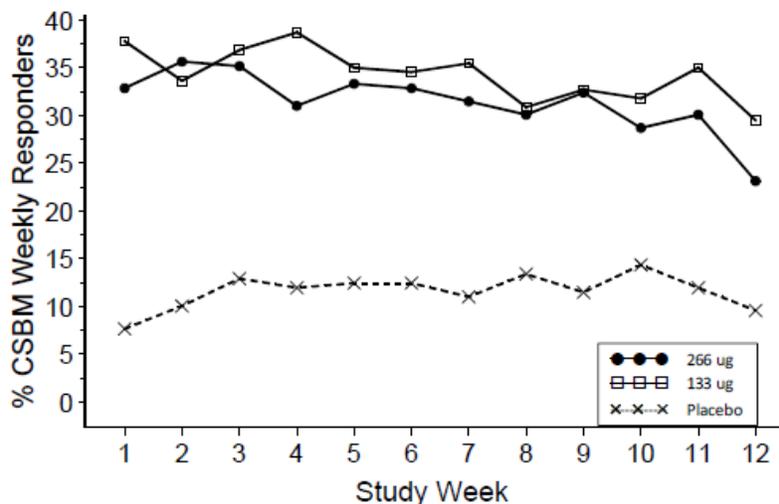
Table 31 Overview of Secondary Efficacy Parameters for the 12-Week Treatment Period Trial MCP-103-303 ITT Population

Change from Baseline	Placebo (N = 209)	Linaclotide 145µg (N = 217)			Linaclotide 290µg (N= 216)		
	LS Mean (SE)	LS Mean (SE)	LSMD (95% CI)	P-value (Significant Under MCP)	LS Mean (SE)	LSMD (95% CI)	P-value (Significant Under MCP)
CSBM Frequency Rate	0.453 (0.169)	1.935 (0.167)	1.482 (1.04, 1.92)	< 0.0001 (Yes)	2.042 (0.167)	1.589 (1.15, 2.03)	< 0.0001 (Yes)
SBM Frequency Rate	1.075 (0.216)	3.034 (0.213)	1.959 (1.40, 2.52)	< 0.0001 (Yes)	2.982 (0.213)	1.907 (1.35, 2.47)	< 0.0001 (Yes)
Stool Consistency	0.576 (0.085)	1.851 (0.084)	1.275 (1.06, 1.49)	< 0.0001 (Yes)	1.838 (0.084)	1.263 (1.04, 1.48)	< 0.0001 (Yes)
Severity of Straining	-0.512 (0.050)	-1.119 (0.050)	-0.606 (-0.74, -0.48)	< 0.0001 (Yes)	-1.150 (0.050)	-0.637 (-0.77, -0.51)	< 0.0001 (Yes)
Abdominal Discomfort	-0.303 (0.037)	-0.478 (0.036)	-0.175 (-0.27, -0.08)	0.0003 (Yes)	-0.435 (0.036)	-0.133 (-0.23, -0.04)	0.0063 (Yes)
Bloating	-0.223 (0.040)	-0.464 (0.040)	-0.240 (-0.34, -0.14)	< 0.0001 (Yes)	-0.373 (0.040)	-0.150 (-0.25, -0.05)	0.0049 (Yes)
Constipation Severity	-0.271 (0.053)	-0.897 (0.053)	-0.626 (-0.76, -0.49)	< 0.0001 (Yes)	-0.810 (0.053)	-0.539 (-0.68, -0.40)	< 0.0001 (Yes)

Source: Modification of Table 12 page 100. Clinical Study Report Trial MCP-103-303. LS=Least Square (mean); LSMD = Least Square Mean Difference (relative to placebo); MCP = multiple comparisons procedure; SE = Standard Error; CI= confidence interval

The applicant provided a graphic depiction of the percentage of patients who were CSBM Weekly Responders as supportive evidence of the primary efficacy parameter. A CSBM Weekly Responder was defined as a patient who had ≥ 3 CSBMs and a change from baseline of ≥ 1 during that particular week. For this analysis, discontinued patients were considered CSBM weekly non-responders for those weeks subsequent to their discontinuation. The proportion of patients who were CSBM Weekly Responder was greater for each dose of Linaclotide over placebo for each of the 12 weeks of the trial. However, there seem to be a slight decline in the response rate over time. This decline was particularly noticeable at the 12 week visit. (See graphic below.)

Figure 7 Percentage of CSBM Weekly Responders during the 12 week Treatment Period Trial MCP-103-303 ITT Population



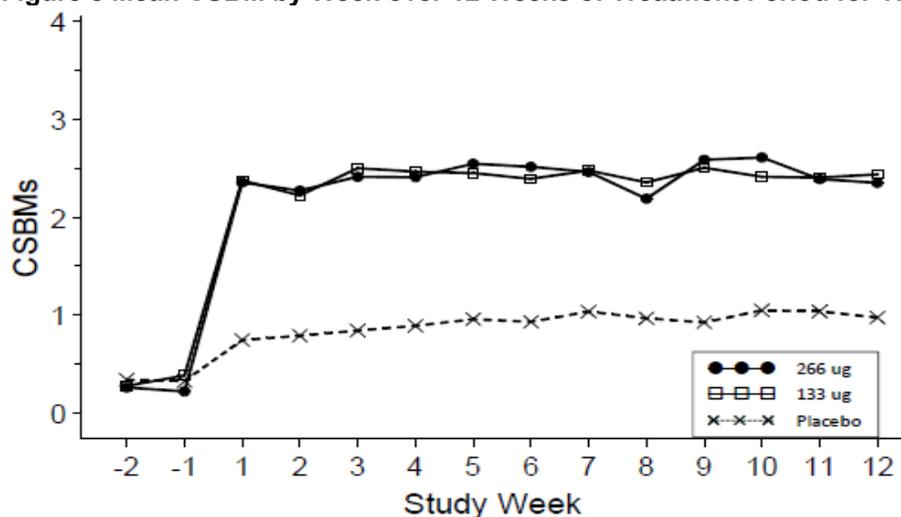
p-values	1	2	3	4	5	6	7	8	9	10	11	12
133 ug	***	***	***	***	***	***	***	***	***	***	***	***
266 ug	***	***	***	***	***	***	***	***	***	**	***	**

* p ≤ 0.05 ** p ≤ 0.01 *** p ≤ 0.001 - p > 0.05
 Weekly p-values were obtained from the CMH test controlling for geographic region, comparing each linaclotide dose versus placebo in a pairwise manner.

Source: Applicant's Figure 4 Clinical Study Report MCP-101-303 p.104

Such a decline would be expected if patients developed a tolerance to the drug's effect, resulting in decreased efficacy. A pattern such as this may also reflect that the number of patients discontinuing the trial (regardless of the reason) increased over time. In other words, as the number of patients who were unable to tolerate the drug fell out of the trial, one would see a decrease in response rates as the non-responder rate increases. However, as previously stated for the most part, the treatment effect appears to be relatively maintained over the 12 weeks of the treatment period. The weekly response rate at 12 weeks may reflect those who were better able to tolerate the drug for a longer period of time or it may reflect decreased efficacy over time as patients developed tolerance to the drug's effects. To sort this out, the reviewer looked at the mean CSBM rate by week and the time to first onset of diarrhea. (The most commonly experienced adverse event leading to discontinuation from the trial was diarrhea. The time from initiation of study drug treatment to the first onset of diarrhea was used to provide an indication of drug tolerability over time.) The mean CSBM rate by week remained fairly steady over the 12 week treatment period suggesting that the drug's treatment effect was maintained for both doses over the 12 weeks of the treatment period. (See graphic below)

Figure 8 Mean CSBM by Week over 12 Weeks of Treatment Period for Trial MCP-103-303 ITT Population



p-values	1	2	3	4	5	6	7	8	9	10	11	12
133 ug	***	***	***	***	***	***	***	***	***	***	***	***
266 ug	***	***	***	***	***	***	***	***	***	***	***	***

* p ≤ 0.05 ** p ≤ 0.01 *** p ≤ 0.001 - p > 0.05
 Weekly p-values for the comparison of each linaclotide dose versus placebo based on an ANCOVA of change from baseline .

Source: Applicant's Figure 6 of the Clinical Study Report for Trial MCP-103-303

In addition, the change from baseline in CSBM Frequency rate remained fairly consistent over each of the 12 weeks of the treatment period for each of the treatment arms. (The average mean change in weekly CSBM frequency rate was 0.6 for the placebo arm; 2.1 for the Linaclotide 145µg arm; and 2.1 for the Linaclotide 290µg arm over the 12 week treatment period.)

However, the number of patients with first onset of a diarrhea treatment emergent adverse event decreased over time. This would suggest that the number of patients who were unable to tolerate the drug decreased over time.

Figure 9 Distribution of the Time to First Onset of Treatment Emergent Diarrhea by Treatment Arm for 12 week Treatment Period Trial MCP-103-303

	Placebo (N=209)		LIN 133 ug (N=217)		LIN 266 ug (N=217)		Lin Total (N=434)	
	n/N (%)	Cum. (%)	n/N (%)	Cum. (%)	n/N (%)	Cum. (%)	n/N (%)	Cum. (%)
Number of Patients with 1st Onset Diarrhea TEAE	14/209 (6.7)		27/217 (12.4)		30/217 (13.8)		57/434 (13.1)	
Time of Initial Onset of Diarrhea								
Day 1	0		4/27 (14.8) (14.8)		5/30 (16.7) (16.7)		9/57 (15.8) (15.8)	
Day 2	3/14 (21.4) (21.4)		4/27 (14.8) (29.6)		3/30 (10.0) (26.7)		7/57 (12.3) (28.1)	
Days 3-7	0		4/27 (14.8) (44.4)		6/30 (20.0) (46.7)		10/57 (17.5) (45.6)	
Week 2	2/14 (14.3) (35.7)		5/27 (18.5) (63.0)		4/30 (13.3) (60.0)		9/57 (15.8) (61.4)	
Week 3	3/14 (21.4) (57.1)		2/27 (7.4) (70.4)		2/30 (6.7) (66.7)		4/57 (7.0) (68.4)	
Week 4	1/14 (7.1) (64.3)		3/27 (11.1) (81.5)		1/30 (3.3) (70.0)		4/57 (7.0) (75.4)	
Week 5	1/14 (7.1) (71.4)		0		4/30 (13.3) (83.3)		4/57 (7.0) (82.5)	
Week 6	0		1/27 (3.7) (85.2)		2/30 (6.7) (90.0)		3/57 (5.3) (87.7)	
Week 7	0		0		0		0	
Week 8	1/14 (7.1) (78.6)		0		1/30 (3.3) (93.3)		1/57 (1.8) (89.5)	
Week 9	0		1/27 (3.7) (88.9)		1/30 (3.3) (96.7)		2/57 (3.5) (93.0)	
Week 10	0		0		1/30 (3.3) (100.0)		1/57 (1.8) (94.7)	
Week 11	1/14 (7.1) (85.7)		2/27 (7.4) (96.3)		0		2/57 (3.5) (98.2)	
Week 12	2/14 (14.3) (100.0)		1/27 (3.7) (100.0)		0		1/57 (1.8) (100.0)	

Source: Applicant's Clinical Study Report for Trial MCP-103-303 Table 14.5.2.7C p 1171

During the trial, patients were allowed to use center – dispensed protocol-defined laxatives (5 mg bisacodyl tablets or 10 mg bisacodyl suppositories) as rescue medication if ≥ 72 hours had passed since the previous bowel movement or when the patient's symptoms became intolerable. Use of rescue medication, or any other laxative, suppositories, or enemas during the treatment period in each Linaclotide dose group was compared to use in the placebo group. The following endpoints for rescue medications were assessed and compared for each of the treatment arms:

- The proportion of patients who reported using per-protocol rescue medications or any other laxative, suppository, or enema
- The proportion of patients who had an increase from baseline in the percentage of days where per-protocol rescue medication or any other laxative, suppository, or enema were used as reported by patients during the treatment period. (Note: The day of randomization was excluded from the calculation of baseline percentages because the use of rescue medications would make a patient ineligible for randomization at the beginning of the study.)
- The change from baseline in the percentage of patient reported days of using rescue medications or any other laxative, suppository or enema

Relative to placebo, the proportion of patients who used rescue medication was lower for both doses of Linaclotide. Likewise the proportion of patients with an increase in the number

of days of rescue medication use was lower in both of the Linaclotide arms relative to placebo. Unlike, Trial LIN-MD-01, least squared mean change from baseline in the percentage of days of rescue medication use was not statistically significant for either Linaclotide dose versus placebo. The results are provided in the table below. The reviewer is referred to the statistical review for additional information

Table 32 Summary of Rescue Medication Use During 12 Week Treatment Period - Trial MCP 103-303 ITT Population

	Placebo (N = 209)	Linaclotide	
		145 µg (N = 217)	290 µg (N = 216)
Patients using Rescue Medication, n (%)	160 (76.6%)	120 (55.3%)	139 (64.4%)
Difference (Linaclotide% – placebo%)	—	-21.3	-12.2
Patients with an increase in number of days of rescue medication use, n (%)	73 (34.9%)	53 (24.4%)	62 (28.7%)
Difference (Linaclotide– placebo)	—	-10.5	-6.2
Change from baseline in percentage of days of rescue medication use			
LSMC from baseline (SE)	-2.842 (1.331)	-3.865 (1.310)	-2.598 (1.310)
LS Mean Difference (Linaclotide– placebo) (95% CI)	0.0093	-1.023 (-4.47, 2.42)	0.244 (-3.21, 3.69)

Source: Reviewer's table modified from Tables 14.4.3.15B, 14.4.3.15C, 14.4.3.15D Clinical Study Report MCP-103-303 LSMC=Least squared mean change, CI = Confidence Interval.

There were 643 randomized patients who received at least 1 dose of Linaclotide during the Treatment Period. These patients comprise the Safety Population. For the Treatment Period, safety analyses were based on the Safety Population. Over 50% of the patients in each treatment arm experienced at least 1 Treatment Emergent Adverse Event (TEAE). More patients in the Linaclotide Arms relative to the Placebo arm experienced a TEAE. Interestingly, the number of patients experiencing an adverse event and the number of adverse events was highest in the group randomized to the lower dose of Linaclotide. This was not seen in Trial LIN-MD-01. A higher percentage of patients in the Linaclotide Arms experienced a Treatment Related Adverse Event (21.7% in the Linaclotide145µg arm; 20.2% in the Linaclotide290µg arm; 14.4% in the placebo arm). Treatment Related Adverse Events include those Adverse Events whose relationship to treatment was assessed by the Investigator as having a “Definite”, “Probable”, or “Possible” relationship to the study drug. The percentage of early withdrawals was comparable across treatment arms. Also, in contrast with Trial LIN-MD-01, a higher percentage of patients in the placebo arm relative to the Linaclotide arms experienced a Serious Adverse Event (2.4% Placebo, 1.4% Linaclotide 145µg, 1.8% Linaclotide 290µg). There were no deaths reported during the conduct of this trial. An overview of the patients experiencing Adverse Events is provided in the table below.

Table 33 Overview of Patients Experiencing Adverse Events During 12 Week Treatment Phase of Trial MCP-103-303 Safety Population

	Placebo N=209	Linaclotide 145µg N = 217	Linaclotide 290µg N = 217
	n (%)	n (%)	n (%)
Total Number of Patients Experiencing an AE by Treatment Arm (TEAE)	105 (50.2%)	122 (56.2%)	119 (54.8%)
Number of Patients Experiencing at least 1 Treatment RELATED Adverse Event [±]	30 (14.4%)	47 (21.7%)	44 (20.3%)
Number of Patients Experiencing Each Category of Adverse Events			
Death	0	0	0
Serious Adverse Event (SAE)	5 (2.4%)	3 (1.4%)	4 (1.8%)
Any AE Resulting in Early Withdrawal	9 (4.3%)	11 (5.1%)	10 (4.6%)

Source: Reviewer's Table

[±] Treatment Related AEs includes those AEs whose relationship to treatment was assessed by the Investigator as "Definite, Probable, or Possible"

Table 34 Overview of Adverse Events Occurring During Treatment Period of Trial MCP-103-303 Safety Population

	Placebo	Linaclotide 145µg	Linaclotide 290µg	Totals
Number of Treatment Emergent Adverse Events By Treatment Arm	204 (27.6%)	273 (36.9%)	262 (35.5%)	739
Category of Adverse Event (percent of totals)				
Death	0	0	0	0
Serious Adverse Event	6 (46.1%)	3 (23.1%)	4 (30.8%)	13
Adverse events leading to discontinuation from trial	9 (23.7%)	17 (44.7%)	12 (31.6%)	38
Adverse events leading to interruption of trial treatment	6 (10.3%)	34 (58.6%)	19 (31.0%)	58

Source: Reviewer's Table generated from Applicant's ADAE dataset Trial MCP-103-303

The reader is referred to the preceding table. An Adverse Event was considered a TEAE if it was not present before the date of the first dose of double-blind study drug for the Treatment Period or if it was present before the date of the first dose of double-blind study drug for the Treatment Period but increased in severity during the specified Treatment Period. (Note: Treatment Emergent Adverse Events occurring during the RW period are not included in this analysis.) There were more TEAEs in both Linaclotide arms when compared to the placebo arm.

The most common treatment emergent adverse events occurring during this trial were from the Gastrointestinal Disorders SOC. Diarrhea was the most commonly reported adverse event occurring in 6.7% of placebo patients, 12.4% of patients taking Linaclotide 145µg and

13.8% of patients taking Linaclotide 290µg. The following table depicts TEAEs reported in at least 3% of patients in either of the Linaclotide arms and at a higher incidence than placebo. As previously mentioned there was splitting of the preferred terms that may describe abdominal pain. With the exception of diarrhea, abdominal distension, most TEAEs were comparable across the treatment arms. A numerically larger proportion of patients in the Linaclotide 290µg group also experienced more TEAEs from the “Infections and Infestations” SOC.

Table 35 TEAEs Experienced in ≥ 3.0% of Either Linaclotide Arm and at an Incidence Greater than Placebo Trial MCP 103-303 Safety Population

	Placebo N = 209	Linaclotide 145µg N = 217	Linaclotide 290µg N = 217
	n (%)		
Patients with at least 1 TEAE	105 (50.2)	122 (56.2)	119 (54.8)
Gastrointestinal disorders	45 (21.5)	58 (26.7)	60 (27.6)
Diarrhea	14 (6.7)	27 (12.4)	30 (13.8)
Nausea	8 (3.8)	7 (3.2)	9 (4.1)
Abdominal distension	3 (1.4)	8 (3.7)	7 (3.2)
Abdominal pain	8 (3.8)	6 (2.8)	9 (4.1)
Abdominal pain upper	3 (1.4)	7 (3.2)	3 (1.4)
Infections and infestations	30 (14.4)	40 (18.4)	36 (16.6)
Nasopharyngitis	6 (2.9)	6 (2.8)	9 (4.1)
Sinusitis	3 (1.4)	2 (2.3)	7 (3.2)
Nervous system disorders	14 (6.7)	14 (6.5)	14 (6.5)
Headache	8 (3.8)	7 (3.2)	10 (4.6)

Source: Reviewer's Table Generated from Applicant's ADAE dataset with modifications from Table 27 Clinical Study Report, Trial MCP-103-303

A total of 11 patients (5.3%) on placebo experienced severe TEAEs, whereas 13 patients (6.0%) in the Linaclotide 145µg group and 15 patients (6.9%) in the Linaclotide 290µg group experienced at least 1 severe TEAE. An overview of the severity of TEAEs occurring during the Treatment period is provided in the table below.

Table 36 Overview of TEAE Severity by Treatment Group Trial MCP 103-303 Safety Population

Number of Treatment Emergent Adverse Events By Treatment Arm	Placebo N = 204 n (% of arm)	LIN 145µg N = 273 n (% of arm)	LIN 290µg N = 262 n (% of arm)	Totals
AE Severity				
Mild	103 (50.4%)	135 (49.5%)	139 (53.1%)	377
Moderate	83 (40.7%)	124 (45.4%)	102 (38.9%)	309
Severe	18 (8.8%)	14 (5.1%)	21 (8.0%)	53

Source: Reviewer's Table

Most of the TEAEs that occurred in each of the treatment arms were mild to moderate in severity. The Linaclotide 145µg treatment arm had the lowest percentage of “Severe” TEAEs.

Relative to placebo, each of the Linaclotide treatment arms had a higher percentage of AEs leading to early withdrawal from the trial or interruption of trial treatment. Interestingly of the two Linaclotide doses, the 145µg Linaclotide arm had a higher percentage of AEs leading to discontinuation or withdrawal relative to the 290µg Linaclotide arm. In some ways, this is consistent with the higher treatment effect that was seen in this trial for the 145µg dose. If the treatment effect is truly higher in the Linaclotide 145 µg group, you would also expect this group to have a higher rate of diarrhea and diarrhea associated adverse events. Indeed, diarrhea was the most common reason for discontinuation in Linaclotide-treated patients, with 7 patients (3.2%) discontinuing due to diarrhea in the 145µg arm and 6 patients (2.8%) discontinuing due to diarrhea in the 290µg arm, compared to 1 patient (0.5%) in the placebo arm.

Of the SAEs that occurred during this trial, the highest percent of SAEs occurred in the placebo arm. In the statistical analysis plan for this trial, an SAE was defined as an “on-therapy SAE” for a specified period if it occurred on or after the date of the first dose of double-blind study drug for the Treatment Period and within 30 days following the date of the last dose of double-blind study drug for the specified period.” By this definition, an SAE could be counted for both the Treatment Period and the RW Period. Therefore, to avoid confusion, SAEs are counted only for the Period in which they occurred.

There were six patients (#0073001, #0223006, #0943018, #0963003, #0283003, #0103011) who experienced an SAE that resulted in early withdrawal during the treatment phase. Two patients experienced at least 1 SAE that was considered by the investigator to be related to study drug. Additional details on these patients are presented in the table below. Patient #0073001, who was on placebo, experienced a moderately severe viral gastroenteritis that resulted in him being discontinued from the trial. Patient #0283003, who took 145µg Linaclotide, was discontinued from the trial secondary to diarrhea and one week later developed mild atrial fibrillation.

The following table provides descriptive summaries of the SAEs that occurred during the Treatment Period of this trial.

Table 37 Descriptive Summaries of Serious Adverse Events During DB Treatment Period Trial MCP-103-303 Safety Population

Subject Number	Treatment Arm	Exact/Reported Term for SAE	MedDRA preferred Term for SAE	Number of Days to SAE Start	Narrative	AE Severity	Investigator Assessment of Relatedness
1073028 (Dropout)	Placebo	Acute Bronchitis	Bronchitis	29	64 year old white female with a history of chronic constipation, heartburn, anxiety, hypertension, depression, asthma, chronic cough, and bipolar disorder. The patient was hospitalized on (b) (6) of study drug treatment after experiencing shortness of breath for (b) (6). At the Screening Visit, she denied having any history of pulmonary disorders and reported taking only oxaprozin and prednisone for arthritis, and trazodone for insomnia. When she was hospitalized the patient admitted to a 3 month history of dyspnea. Physical exam was significant for mild expiratory wheezing. Work-up during hospitalization (including chest Xray and CT) was unremarkable. The patient was treated with IV steroids, antibiotics and oxygen for an acute bronchitis and with pantoprazole for heartburn. During hospitalization, the patient was started on bisoprolol for hypertension and duloxetine for depression was restarted. Discharge diagnoses included acute bronchitis (felt to be a viral bronchitis), bipolar disorder, anxiety, hypertension, insomnia, and osteoarthritis. discharge medications included alprazolam, bisoprolol, duloxetine, montelukast, pantoprazole, salbutamol, seretide, tussionex, and valproate semisodium. The acute bronchitis resolved on trial Day 31. By trial Day 37 (Week 4 Visit), patient had improved but the dyspnea was considered ongoing. All labs were normal with the exception of an elevated total cholesterol and creatinine. The patient discontinued study drug on Day 46 (reason unknown) and was lost to follow-up.	Moderate	Unrelated
0963003 (Dropout)	Placebo	Atrial Fibrillation	Atrial Fibrillation	29	68 year old white male with past medication history of chronic constipation, benign prostatic hyperplasia, hypertension, hypothyroidism, Type 2 diabetes mellitus, hiatal hernia. Patient was for (b) (6) hospitalized beginning trial (b) (6) (Week 4 Visit) after an ECG performed during the trial visit revealed atrial fibrillation with controlled ventricular response. An ECG at the hospital confirmed that the patient had atrial fibrillation. Review of systems was negative. Physical examination was significant for bilateral carotid bruits (left>right). (The narrative stated that the patient had a normal heart rate, however this would be inconsistent with the diagnosis of atrial fibrillation.) Labs were unremarkable. Creatine phosphokinase was negative and troponin levels were normal. Chest xray was normal. TSH was normal. The patient was treated with enoxaparin and warfarin for the A. fib. The patient was discontinued from the trial on trial Day 32. At the end of termination visit on trial Day 39, physical exam and all labs were normal. Triplicate ECG showed sinus bradycardia. The SAE was considered to be resolved on Day 39, however the patient was lost to follow-up.	Moderate	Unlikely

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Subject Number	Treatment Arm	Exact/Reported Term for SAE	MedDRA preferred Term for SAE	Number of Days to SAE Start	Narrative	AE Severity	Investigator Assessment of Relatedness
0943018 (Dropout)	Placebo	Left inferior parathyroid adenoma	Parathyroid tumour benign	67	61 year old white female with chronic constipation, hypertension, hemorrhoids, right ear deafness. The patient was s/p hysterectomy. Patient was found to have a benign parathyroid tumor after labs showed an elevated serum calcium and parathyroid hormone levels. An ultrasound on trial (b) (6) was consistent with a parathyroid tumor. The Investigator reported the elevated blood calcium began trial Day -33 (Screening). The patient underwent a parathyroidectomy of a left inferior parathyroid adenoma. Postoperatively the patient did well and PTH level returned to normal. The patient took her last dose of study drug on trial Day 67 when she was discontinued from the study. At the termination visit (Day 72), physical exam and labs were normal with the exception of elevated total cholesterol.	Mild	Unrelated
0223006 (No Action) (Dropout)	Placebo	Community Acquired Pneumonia	Pneumonia	57	85 year old white male with an extensive past medical history that included chronic constipation, diverticulosis, hemorrhoids, gallstones, pancreatic atrophy, rectal adenoma, hypercholesterolemia, hyperglycemia, hypertension, atrial fibrillation. Patient was s/p septal myocardial infarction. On trial (b) (6) (Week 8 visit), an ECG revealed atrial fibrillation, deemed a clinically significant change from baseline. The patient was withdrawn from the trial on Day 57. The patient was sent to the hospital where he reported a 3 to 4 day history of fatigue, malaise, shortness of breath, and cough productive of thick yellow sputum. ECT at the hospital showed atrial fibrillation with a rapid ventricular response, aberrant conduction, ventricular premature complexes, non-specific ST and T wave abnormality, and probable digitalis effect (?). Cardiac enzymes were within normal limits. Chest Xray showed bibasilar opacities with small bilateral effusions. Physical was significant for diffuse expiratory wheezing and decreased breath sounds at the base of both lungs. Patient was admitted on trial Day 58 for pneumonia evaluation. Sputum cultures were negative. Labs were significant for low protein, low albumin, leucopenia, anemia, and thrombocytopenia. On physical exam, the patient was mildly hypoxic but did not require oxygen. The patient was treated with IV antibiotics and albuterol/ipratropium for the pneumonia. The atrial fibrillation was treated with metoprolol. The atrial fibrillation was reported to have resolved on trial Day 59. The last dose of study drug was taken trial Day 57. At the termination visit (Day ?) ECG and lab results were not clinically significant. The pneumonia was reported to have resolved on what would be considered trial Day 80.	Severe	Unrelated
	Placebo	Worsening Atrial Fibrillation with Rapid Ventricular Response	Atrial Fibrillation			Severe	Unrelated

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Subject Number	Treatment Arm	Exact/Reported Term for SAE	MedDRA preferred Term for SAE	Number of Days to SAE Start	Narrative	AE Severity	Investigator Assessment of Relatedness
0073001 (Dropout)	Placebo	Viral gastroenteritis	Gastroenteritis viral	21	30 year old white female with a history of hypertension, depression, anxiety, chronic constipation, GERD. Patient was s/p tubal ligation and cholecystectomy. Meds included Wellbutrin XL, Amlodipine/Benazepril, and Vistaril. On trial (b) (6) the patient was hospitalized after she developed nausea, vomiting, abdominal pain, and bloody diarrhea. She was withdrawn from the trial on Day 21. At the time her white blood cell count was elevated with elevated neutrophils on the differential. Physical exam findings were not reported. Review of systems was negative except for the gastrointestinal symptoms mentioned previously. A CT scan with contrast was consistent with infectious or inflammatory colitis. A flexible sigmoidoscopy revealed a normal colon with no evidence of colitis or bleeding. Stool was negative for ova and parasites, Giardia and Cryptosporidium antigen and C. difficile toxin. The patient was treated with IV fluids, pain medication, and anti-emetics. The patient had not bloody diarrhea after hospital admission. It was noted that menses began on (b) (6) before hospitalization. Patient was discharged with a diagnosis of viral gastroenteritis with bloody diarrhea, consistent with infectious colitis and dehydration. Patient took her last dose of study drug on trial Day 21. The gastroenteritis was reported to have resolved on what would have been considered trial Day 27 (6 days after onset). At the termination visit on Day 50, physical exam, ECG and labs were normal.	Moderate	Possible
0663003 (Treatment Interrupted)	Linacotide 145 µg	Nonspecific chest pain	Chest Pain	82	60 year old white female smoker with a history of hypothyroidism, drug hypersensitivity, seasonal allergies, and insomnia. Patient was s/p appendectomy and cholecystectomy (b) (6). Medications included aspirin, levothyroxine and Norel Ex for allergic rhinitis. On trial (b) (6), the patient was hospitalized for nonspecific chest pain in the epigastric area and radiating toward the central chest. On admission, physical exam was unremarkable except for tenderness in the epigastric region. An ECG showed sinus arrhythmia and first degree atrioventricular block. Cardiac enzyme levels were normal, and telemetry was negative. Patient complained of nausea and anxiety while hospitalized. The chest pain was treated with nitroglycerin and morphine sulfate. She was also given aluminum hydroxide/magnesium hydroxide/simethicone for her heartburn and indigestion; prochlorperazine for nausea; alprazolam for anxiety, milk of magnesia constipation; esomeprazole for gastritis; nicotine patch for smoking cessation; and aspirin for first degree atrioventricular block. The patient was discharged on hospital (b) (6). Discharge diagnoses included epigastric pain, gastritis, and nonspecific chest pains (cause unknown). All of the patient's complaints resolved by trial Day 84 with the exception of the atrioventricular block was considered ongoing. Study drug treatment was temporarily interrupted on trial day 83 but resumed on trial Day 84. The patient completed the trial.	Mild	Unrelated

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Subject Number	Treatment Arm	Exact/Reported Term for SAE	MedDRA preferred Term for SAE	Number of Days to SAE Start	Narrative	AE Severity	Investigator Assessment of Relatedness
1103005	Linaclotide 145µg	Pneumonia	Pneumonia	82	72 year old white female with a past medical history of chronic constipation, GERD, chest pain, osteoporosis, hypertension, hyperlipidemia, coronary artery disease (s/p myocardial infarction) left bundle branch block, allergies, hemorrhoids, gallstones. Patient experienced a stroke prior to enrolling in the trial. (This reviewer noted that the patient was bradycardic on 8 of the Trial Visit Days.) Patient was hospitalized for (b) (6) of the trial) for pneumonia. The pneumonia was associated with cough, dyspnea, left sided pain, fever, chills, and a mild nasopharyngitis that began on study Day 75. Physical exam on admission was significant for fever, tachycardia (pulse 109), respiratory rate of 18, and decreased breath sounds with rales in the left lung. Chest xray showed an infiltrate in the left lower lobe. ECG showed sinus tachycardia and was consistent with left atrial dilatation and left bundle branch block. White count was elevated with increased neutrophils, The patient was treated with IV fluids, IV antibiotics, and nebulizer treatments for the pneumonia. She was also given treatment for pain, fever, and pleurisy (steroids). The patient developed mild hyperglycemia secondary to steroid use and was treated with insulin. She was also started on metoprolol for hypertension. Discharge medications included budesonide with foterol fumarate, levofloxacin, prednisone, and ramipril. The pneumonia SAE was considered resolved on Day 85 after a chest X-ray demonstrated no evidence of any infiltrate. The hyperglycemia and hypertension also resolved on trial Day 85. The sinus tachycardia TEAE resolved on Day 90. Study drug dosing was not interrupted. The patient completed the Treatment Period on Day 90 enrolled into the RW Period. (Note: Chest xray findings tend to lag behind clinical improvement in patients who experience pneumonia. The quick resolution of initial chest x-ray findings may indicate that the patient had another pulmonary process.) This patient also experienced a serious adverse event of pulmonary embolism during the RW phase. Please refer to that section for additional details.	Moderate	Unrelated

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Subject Number	Treatment Arm	Exact/Reported Term for SAE	MedDRA preferred Term for SAE	Number of Days to SAE Start	Narrative	AE Severity	Investigator Assessment of Relatedness
0283003 (Dropout)	Linaclotide 145µg	Atrial Fibrillation	Atrial Fibrillation	11	78 year old White male with a history of chronic constipation, epigastric discomfort, hemorrhoids, left colon diverticulosis, inguinal hernia, cholelithiasis, H. pylori infection, urinary hesitancy, sleep apnea, and hypertension. Patient was s/p multiple surgeries. Patient developed moderate diarrhea on trial Day 1 of study drug treatment which resolved by trial Day 5, when treatment was stopped and the patient was discontinued from the trial. At the termination visit on trial Day 11, an ECG revealed atrial fibrillation with a controlled ventricular response and poor R wave progression. he was sent to an urgent care center where ECGs confirmed the presence of the atrial fibrillation (with controlled ventricular response) and poor R wave progression. In the urgent care center, the patient complained of slight dyspnea but denied any lightheadedness, syncope, chest pain, palpitations, or edema. Labs were normal. The patient was started on warfarin. A 2-D echocardiogram with color Doppler flow revealed borderline hypertrophy of the left ventricle with normal systolic functioning (ejection fraction 62%). The echo also demonstrated elevated filling pressure, Grade III left ventricular diastolic dysfunction, disproportionate upper septal thickening, and a mildly dilated left atrium/appendage with increased pressure. The right ventricle, right atrium, aortic valve, pulmonic valve, aorta, interatrial septum, and pericardium were all normal; however, there was mild regurgitation of the mitral valve and tricuspid valve (grade +1). The atrial fibrillation SAE was considered resolved on Day 16 after a 24-hour Holter monitor revealed sinus rhythm, an average heart rate of 71 bpm (range 46 to 150 bpm), and no evidence of atrial fibrillation.	Mild	Possibly

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Subject Number	Treatment Arm	Exact/Reported Term for SAE	MedDRA preferred Term for SAE	Number of Days to SAE Start	Narrative	AE Severity	Investigator Assessment of Relatedness
1033017 (Drop out)	Linaclotide 290µg	Diverticular Bleed Unknown Location in Colon	Diverticulum intestinal hemorrhagic	7	68 year old female African-American female hospitalized for 7 days beginning on (b) (6). Past medical history significant for chronic constipation, diverticulosis, hemorrhoids, GERD, peptic ulcer disease, arthritis, carpal tunnel syndrome, macular degeneration, normal pressure hydrocephalus, and asthma. Patient was post-menopausal and s/p antrectomy, VP shunt placement, and vagotomy. Medications included aspirin, Celebrex, Neurontin, Singulair, Maxair, Ranitidine, Albuterol, Advair, and Nasacort. On (b) (6) the patient presented to the hospital with rectal bleeding following a difficult bowel movement. No diarrhea reported. Physical exam and chest xray were unremarkable. Labs revealed a low hematocrit (26.6%). Colonoscopy revealed clots and fresh blood in the anus, multiple diverticula throughout the colon, blood clots and bright red blood throughout her colon. Per report, there were no polyps, arteriovenous malformations, or other lesions, and no evidence of ischemic colitis. Upper endoscopy was unremarkable except for the missing antrum. The patient was transfused with packed red blood cells and given bisacodyl and docusate. The aspirin and Celebrex were stopped and patient was given paracetamol for her arthritis. The diverticular bleed resolved on what would be considered Trial Day 14. Patient was withdrawn from the study because of the history of antrectomy (an exclusion criterion). Last dose of study drug was trial Day 8. At the termination visit all labs were normal.	Severe	Unlikely
0473003 (Treatment Interrupted)	Linaclotide 290µg	Cerebral Vascular Accident	Cerebrovascular Accident	49	69 year old African-American female. Past medical history of hyperlipidemia, hypertension, hemorrhoids, osteoarthritis, chronic constipation, recurrent urinary tract infection. Prior medications included Lipitor, Calcium, Fish Oil, and Vitamin B complex. Past surgeries included a prior hysterectomy and cholecystectomy. Patient was hospitalized for 5 days beginning trial (b) (6), after she presented with double vision and dizziness. A venous Doppler of the lower extremities, bilateral carotid duplex imaging, and a chest X-ray were normal. Head CT was negative. Brain MRI showed a solid focal acute to subacute thalamic ischemic infarct involving the right medial thalamus. Magnetic resonance angiography (MRA) of the neck and brain, and an MRI of the orbits were normal. Urinalysis was positive for leukocytes and bacteria. The patient was treated with IV fluids, with aspirin, valium, ibuprofen, acetaminophen and hydrocodone, paracetamol, ranitidine, zolpidem tartrate, dipyridamole and levofloxacin. Discharge diagnoses included a cerebral vascular accident, diplopia (most likely secondary to right medial thalamic infarct), urinary tract infection, dehydration, and azotemia. All treatment emergent adverse events were resolved by trial Day 53. Study drug was resumed on trial day 56, after being held from trial Days 50 – 55). Patient was able to complete the study	Moderate	Unrelated

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Subject Number	Treatment Arm	Exact/Reported Term for SAE	MedDRA preferred Term for SAE	Number of Days to SAE Start	Narrative	AE Severity	Investigator Assessment of Relatedness
0103011 (Dropout)	Linaclotide 290µg	Left Ectopic Pregnancy	Ectopic Pregnancy	82	40 year old African-American female with a history of hyperlipidemia, arteriovenous malformation of the cecum, and bilateral tubal ligation. Concomitant medications included aspirin for thrombosis prevention. On trial Day 82, patient reported that she missed her menstrual cycle. Urine pregnancy was positive and a pelvic ultrasound revealed an ectopic pregnancy in the left fallopian tube. Her beta-hCG was elevated at 40,000 mIU/ml. The patient was withdrawn from the study. The ectopic was removed surgically via laparoscopic left salpingo-oophorectomy as an outpatient procedure on (b) (6) and the SAE was considered resolved. At the termination visit on what would be considered trial Day 85, the patient was allocated to the RW period. However, before she took study drug, it was decided that she should withdraw from the study due to the SAE.	Severe	Unrelated
0013004	Linaclotide 290µg	Left Hand Cellulitis	Cellulitis	53	58 year old White post-menopausal female with a past medical history of chronic constipation (b) (6), osteoarthritis, s/p hysterectomy. The only concomitant medication was Etodolac. On Trial (b) (6) patient was seen in the ER for evaluation and management of left wrist pain following a fall. She was diagnosed with a joint sprain and treated with IV fentanyl, hydromorphone hydrochloride, and ketorolac tromethamine for pain. The patient returned to the ER the following day after developing pain, redness, and swelling at the IV site. On physical exam, the patient had tenderness of the left hand and left shoulder, was unable to lift her left arm above her head, and had pain on active and passive rotation of the left arm. An X-ray was negative for a fracture. Labs were significant for an elevated C-reactive protein level, a high sedimentation rate and a borderline elevated WBC count. She was diagnosed with a cellulitis and treated with IV antibiotics, morphine, and acetaminophen/codeine for the wrist pain. She was discharged with oral Keflex and Panadeine for pain. The left hand cellulitis resolved by trial Day 55. On trial Day 56, a left extremity cellulitis was reported for the patient that resolved on trial day 59. Joint pain resolved by trial Day 77. Study drug was continued throughout the treatment for the cellulitis and the patient completed the trial	Severe	Unrelated

Source: Reviewer's Table Generated from ADAE Dataset from MCP-103-303 with modifications from

More patients in the Linaclotide arms experienced diarrhea and rated their diarrhea as severe. Fourteen patients (6.7%) in the placebo group had diarrhea. Diarrhea was reported in 27 patients (12.4%) in the 145µg Linaclotide group and 30 patients (13.8%) in the 290µg Linaclotide dose group. Three patients (1.4%) in each Linaclotide dose group had severe diarrhea compared with 1 patient (0.5%) in the placebo group who had severe diarrhea. The median time to onset from first dose of study drug treatment to the first episode of diarrhea was 17 days for placebo, 12 days for Linaclotide 145µg, and 11 days for Linaclotide 290µg. The incidence of treatment emergent diarrhea appeared to decrease over time.

The incidence of adverse events leading to early patient withdrawal is presented by preferred term for each of the treatment arms. Diarrhea was the most common adverse event leading to discontinuation in the Linaclotide treatment arms. The incidence of diarrhea was similar for both doses (3.2% for Linaclotide 145µg, 2.8% for Linaclotide 290µg)

Table 38 Incidence of Adverse Events Leading to Early Withdrawal by Treatment Arm and Preferred Term during Treatment Period Trial MCP-103-303

	Placebo N=209	LIN 145µg N = 217	LIN 290µg N = 217
	n (%)	n (%)	n (%)
Number of Patients Experiencing Adverse Events Resulting in Early Withdrawal	8 (3.8%)	12 (5.5%)	12 (5.5%)
Number of Patients Experiencing each AE by Preferred term (% of total arm)			
Diarrhea	1 (0.5)	7 (3.2)	6 (2.8)
Abdominal Pain	2 (1.0)	1 (0.5)	2 (0.9)
Abdominal Pain upper	0	2 (0.9)	0
Abdominal Distension	0	1 (0.5)	0
Blood glucose increased	0	0	1 (0.5)
Dyspepsia	0	1 (0.5)	0
Ectopic Pregnancy	0	0	1 (0.5)
Fecal incontinence	0	1 (0.5)	0
Flatulence	0	1 (0.5)	0
Gastroesophageal reflux disease	0	1 (0.5)	0
Headache	0	1 (0.5)	0
Hyperemia	0	0	1 (0.5)
Nausea	0	1 (0.5)	0
Vision Blurred	0	0	1 (0.5)
Atrial Fibrillation	2 (1.0)	0	0
Carotid bruit	1 (0.5)	0	0
Viral gastroenteritis	1 (0.5)	0	0
Myalgia	1 (0.5)	0	0
Parathyroid tumor benign	1 (0.5)	0	0

Source: Reviewer's Table Generated from ADAE dataset

Descriptive statistics were used to describe the changes from baseline in physical exam findings, vital signs, and laboratory values. Overall there were no trends or clinically

meaningful differences between the placebo group and the two Linaclotide groups for any of the laboratory parameters, or physical exam findings. This is not surprising, given that the drug has low systemic availability. The following tables reproduced from the applicant's submission, summarize the changes from baseline in electrolytes and vital signs. Because Linaclotide may induce a secretory diarrhea, particular attention was given to Sodium, Potassium, Chloride, and Bicarbonate levels. In reviewing vitals signs, the reviewer assessed for significant drops in blood pressure and increases in heart rate to assess for orthostatic hypotension. The reviewer also assessed for changes in hematology parameters that may be suggestive of anemia as part of the ischemic colitis assessment and for decreases in leukocytes (especially absolute neutrophil count and absolute lymphocyte count). This was done because drops in leukocytes were observed in Trial LIN-MD-01 and the SOC "Infections and Infestations" had an incidence of TEAEs over 15% for each of the treatment arms for that trial. (Specifically, the percentage of patients who experienced a TEAE from the "Infections and Infestations" was 18.7% for placebo, 22.8% for Linaclotide 145µg and 19.4% for Linaclotide 290µg.) Interestingly, the trends in the potentially clinically significant post-baseline changes in absolute lymphocyte count and absolute neutrophil count were not as apparent in Trial MCP-103-303.

Overall there were no clinically significant trends observed across the treatment arms. There were no meaningful differences among the treatment groups with respect to incidence of abnormal laboratory results reported as treatment emergent AEs. Only 1 patient treated with Linaclotide had an abnormal laboratory result reported as a treatment emergent adverse event that was considered possibly, probably, or definitely related to study drug. That patient had been treated with 145µg of Linaclotide and experienced an increase in blood calcium. The majority of patients in all treatment groups did not have clinically significant changes in hematology and the reviewer could not detect trends. There were no meaningful differences between placebo and each of the Linaclotide groups in vital signs. Less than 2% of patients in all of the study treatment groups had an abnormal laboratory finding for hematology, chemistry, or urinalysis reported as a treatment emergent adverse event during the Treatment Period. Please refer to the tables below.

Table 39 Changes from Baseline in Electrolytes at End of Treatment Trial MCP-103-303 Safety Population

Parameter	Placebo (N = 209)		Linaclotide			
			145 µg/day (N = 217)		290 µg/day (N = 217)	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Calcium, mmol/L						
Baseline	206	2.4 ± 0.1	213	2.4 ± 0.1	211	2.4 ± 0.1
End of study	206	2.4 ± 0.1	213	2.4 ± 0.1	211	2.4 ± 0.1
Change	206	0 ± 0.1	213	0 ± 0.1	211	0 ± 0.1
Chloride, mmol/L						
Baseline	205	102.9 ± 2.6	213	103.4 ± 2.5	211	103.2 ± 2.3
End of study	205	103.1 ± 2.5	213	103.4 ± 2.5	211	103.3 ± 2.6
Change	205	0.2 ± 2.5	213	0 ± 2.2	211	0.1 ± 2.3
Magnesium, mmol/L						
Baseline	206	0.9 ± 0.1	213	0.9 ± 0.1	210	0.9 ± 0.1
End of study	206	0.9 ± 0.1	213	0.9 ± 0.1	210	0.9 ± 0.1
Change	206	0 ± 0.1	213	0 ± 0.1	210	0 ± 0.1
Phosphorus, mmol/L						
Baseline	205	1.2 ± 0.2	213	1.2 ± 0.2	210	1.2 ± 0.2
End of study	205	1.1 ± 0.2	213	1.1 ± 0.2	210	1.2 ± 0.2
Change	205	-0.1 ± 0.2	213	-0.1 ± 0.2	210	-0 ± 0.2
Potassium (mmol/L)						
Baseline	205	4.2 ± 0.5	213	4.2 ± 0.4	210	4.2 ± 0.4
End of study	205	4.2 ± 0.4	213	4.2 ± 0.4	210	4.2 ± 0.4
Change	205	0 ± 0.4	213	0 ± 0.4	210	0 ± 0.4
Sodium, mmol/L						
Baseline	205	139.2 ± 2.2	213	139.3 ± 2.0	211	139.4 ± 2.1
End of study	205	139.3 ± 2.3	213	139.3 ± 1.9	211	139.1 ± 2.1
Change	205	0.1 ± 2.0	213	0 ± 1.9	211	-0.2 ± 2.1

Source: Reviewer's Table Modified from Table 14.5.4.7A Applicant's Clinical Study Report page1637

Note: Baseline is defined as the last non-missing assessment prior to first dose of double-blind study drug. End of Study is the last non-missing assessment in the treatment period. Only patients with baseline and at least one postbaseline assessment are included.

Table 40 Mean Changes from Baseline Vital Signs Trial MCP-103-303 Safety Population

Parameter	Placebo (N = 209)		Linaclotide			
			145 µg/day (N = 217)		290 µg/day (N = 217)	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Derived Systolic blood pressure, mm Hg						
Baseline	209	122.4 ± 14.5	214	120.4 ± 13.9	215	121.7 ± 17.1
End of study	209	120.1 ± 13.8	214	119.4 ± 14.1	215	120.1 ± 15.2
Change	209	-2.3 ± 13	214	-0.9 ± 12.1	215	-1 ± 14.8
Derived Diastolic blood pressure, mm Hg						
Baseline	209	75.9 ± 8.7	214	75.4 ± 9.1	215	75.3 ± 8.9
End of study	209	75.2 ± 9.3	214	75.1 ± 9.1	215	75.2 ± 9.3
Change	201	-0.7 ± 9.2	214	-0.3 ± 7.9	215	-0.1 ± 8.8
Pulse rate, beats per minute						
Baseline	209	70.7 ± 9.5	215	71.1 ± 8.5	215	71.4 ± 10.5
End of study	209	71.6 ± 10.7	215	72.6 ± 9.6	215	72.5 ± 9.9
Change	209	0.9 ± 10	215	1.5 ± 9.3	215	1.1 ± 10
Body weight, kg						
Baseline	209	77.1 ± 17	215	76.5 ± 18.8	215	76.8 ± 15.9
End of study	209	77.2 ± 17.3	215	76.6 ± 18.8	215	76.7 ± 16.1
Change	209	0.0 ± 2.0	215	0.1 ± 2.2	215	-0.1 ± 2.0

Source: Reviewer's Table derived from Applicants ADVS dataset and Tables 14.5.5.4A, 14.5.5.5A, 14.5.5.6A
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There were no appreciable clinically significant differences in blood pressure, pulse, and body weight between each of the treatment arms. There were 2 patients who had increased weight reported as a treatment emergent adverse event. Patient #0213004 in the 145µg Linaclotide dose group experienced possibly-related weight gain that was moderate in severity and Patient #0633017 in the placebo dose group experienced possibly-related mild weight gain. Neither of these patients met the pre-specified criteria for potentially clinically significant weight gain (i.e. weight gain above 7%). One patient in the placebo group, 2 patients in the 145µg Linaclotide group and 2 patients in the 290µg Linaclotide group experienced fever. All were considered mild to moderate in severity and unrelated to study drug treatment. The incidence of patients experiencing potentially clinically significant changes in laboratory values is presented in the table below.

Table 41 Number of Patients & Incidence of Potentially Clinically Significant Clinical Laboratory Values (Hematology and Chemistry) During the Treatment Period for Trial MCP-103-303

Laboratory Parameter	PCS Criteria	Placebo N = 290 n/N1 (%)	Linaclotide	
			145 µg/day N = 217 n/N1 (%)	290 µg/day N = 217 n/N1
Hematology				
Hematocrit (Ratio)	< 0.9 × LLN	2/202 (1.0)	1/212 (0.5%)	0/210
	>1.1 X ULN	0/202	0/212	0/210
Hemoglobin	< 0.9 × LLN	2/202 (1.0)	1/212 (0.5)	1/208 (0.5)
	>1.1 X ULN	0/202	1/212 (0.5)	0/208
Absolute lymphocyte cell count (10 ⁹ / L)	> 1.5 × ULN	0/203	0/213	0/210
	< 0.8 × LLN	5/203 (2.5)	7/213 (3.3)	3/210 (1.4%)
Absolute neutrophil cell count (10 ⁹ / L)	> 1.5 × ULN	0/203	1/210 (0.5)	1/206 (0.5)
	< 0.8 × LLN	5/203 (2.5)	1/210 (0.5)	1/206 (0.5)
Platelet count (10 ⁹ / L)	> 1.5 × ULN	0/206	0/212	0/209
	< 0.5 × LLN	0/206	0/212	0/209
Red blood cell count (10 ¹² / L)	> 1.1 × ULN	0/206	1/213 (0.5)	0/210
	< 0.9 × LLN	1/206 (0.5)	1/213 (0.5)	1/210 (0.5)
White blood cell count (10 ⁹ / L)	> 1.5 × ULN	0/206	0/212	0/211
	<0.7 x LLN	1/206 (0.5)	1/212 (0.5)	0/211
Chemistry				
Alanine aminotransferase	≥ 3 × ULN	0/206	0/212	1/211 (0.5)
Albumin	< 0.9 x LLN	1/205 (0.5)	0/213	0/210
	> 1.1 × ULN	1/205 (0.5)	0/213	0/210
Aspartate aminotransferase	≥ 3 × ULN	1/206 (1.0)	1/213 (0.5)	0/211
Bilirubin, total(mmol/L)	> 1.5 × ULN	2/206 (1.0)	1/212 (0.5)	0/211
Blood urea nitrogen (mmol/L)	> 1.2 × ULN	2/205 (1.0)	1/213 (0.5)	2/211 (0.9)
Cholesterol	> 1.6 × ULN	1/205 (0.5)	0/211	1/210 (0.5)
Creatinine	> 1.3 × ULN	2/205 (1.0)	0/212	1/211 (0.5)
Glucose, nonfasting (mmol/L)	<0.8 X LLN	2/202 (1.0)	2/212 (0.9)	0/207
	>1.4 X ULN	1/202 (0.5)	1/212 (0.5)	3/207 (1.4)

Source: Reviewer's Table Derived from Applicant's Tables 33 and Tables 14.5.4 2A Clinical Study Report Trial MCP-103-303.

PCS = Potentially clinically Significant

N = Number of patients randomized to that treatment arm.

N1 = Number of patients with available non-baseline value and at least 1 post baseline assessment

n = Number of Patients (of the N1 patients) who met PCS criteria at least once during the Treatment Period

U LN= Upper Limit of Normal

LLN= Lower Limit of Normal

The majority of patients did not have potentially clinically significant values for hematology and chemistry. The reviewer did not appreciate any trends in values when comparing the placebo and Linaclotide arms.

Table 42 Number and Incidence of Patients with Potentially Clinically Significant Electrolyte Values During the Treatment Period for Trial MCP-103-303

Laboratory Parameter	PCS Criteria	Placebo N = 290 n/N1 (%)	Linaclotide	
			145 µg/day N = 217 n/N1 (%)	290 µg/day N = 217 n/N1
Electrolytes				
Chloride (mmol/L)	<0.9 X LLN	0/206	0/213	0/211
	> 1.1 x ULN	0/206	0/213	0/211
Sodium (mmol/L)	< 0.9 x LLN	0/206	0/213	0/211
	> 1.1 x ULN	0/206	0/213	0/211
Bicarbonate (mmol/L)	< 0.9 x LLN	0/206	0/213	0/211
	> 1.1 x ULN	0/206	0/213	0/211
Calcium (mmol/L)	<0.9 X LLN	0/205	0/213	0/211
	> 1.1 x ULN	0/205	0/213	0/211
Potassium (mmol/L)	<0.9 X LLN	1/201 (0.5)	2/211 (0.9)	3/210 (1.4)
	> 1.1 x ULN	0/201	0/211	1/210 (0.5)

Source: Reviewer's Table Derived from Applicant's Tables 33, Tables 14.5.4.2A Clinical Study Report Trial MCP-103-303.

PCS = Potentially clinically Significant

N = Number of patients randomized to that treatment arm.

N1 = Number of patients with available non-baseline value and at least 1 post baseline assessment

n = Number of Patients (of the N1 patients) who met PCS criteria at least once during the Treatment Period

ULN= Upper Limit of Normal

LLN= Lower Limit of Normal

Overall there were no appreciable trends in potentially clinically significant changes in electrolytes. Potentially clinically significant changes were seen only in measures of potassium. However, changes occurred in all arms and the overall incidence was very low.

Single 12-lead ECGs were performed at Screening and upon trial completion. A subset of patients had triplicate ECGs performed. According to the applicant, for this subset of patients, an average of the 3 consecutive ECG values for each measurement at each visit was used to generate summary statistics. Measurements were recorded for the PR interval, QRS duration, RR interval, QT interval, RR interval, QT_c interval Bazett, and QT_c interval Fridericia. Overall the mean changes in each ECG parameter after dosing with study drug were not clinically meaningful.

In addition to the single 12-lead ECGs, 280 patients in the Safety Population participated in the triplicate ECG program to determine if Linaclotide had effects on the QT/QTc interval. There were no mean QTc values (Bazett or Fridericia) of > 500 msec. According to the applicant, "Three patients in the triplicate ECG cohort had individual QTc values of > 500msec during the Treatment Period (e.g., only 1 of the triplicate ECGs in each case showed the abnormality) Patient #0333004 in the placebo group had a QTc interval (Fridericia) of 505 msec at the Day 15 visit (Baseline value 488.7);

Patient #0183007 in the Linacotide 145µg group had a QTc interval (Bazett) of 504 msec at the Day 57 visit (Baseline value 465); and Patient #1023007 in the Linacotide 145µg group had a QTc interval (Bazett) of 506 msec at the Day 85 visit (Baseline value 465.7). No patients in the Linacotide 290 µg dose group had an individual QTc value > 500 msec in the Treatment Period.”

Overall there were nine patients who experienced potentially clinically significant post-baseline ECG values during the treatment period. Of these, 6 were in the placebo arm and 3 were in the Linacotide 145µg arm (patient #0863008 had a widened QRS interval of 154; patients #0183007 and #1023007 had prolonged QT_c intervals >500msec). These changes did not appear to be associated with electrolyte changes. The overall incidence of post-baseline potentially clinically significant ECG values was < 1% in the Linacotide 145µg group. There were no patients in the Linacotide 290µg dose group who experienced a potentially significant ECG change.

At the end of the Treatment Period, there were two patients (patient #0283003 and patient #0663003) in the Linacotide 145µg who had abnormal clinically significant shifts in ECG parameters. Patient #0283003 was a 78 year old white male and patient #0663003 was a 60 year old white female. Both patients were treated with Linacotide 145µg and had normal baseline ECGs that became abnormal and clinically significant at the end of the Treatment period. In addition there was a third patient (not included in the table) with a *potentially* clinically significant abnormal ECG value in the Linacotide 145µg group. Patient #0753003, a 69 year old white male, had an abnormal nonclinically significant ECG at baseline that remained abnormal and nonclinically significant at the end of the treatment period. At the time of the 16 week trial completion this patient’s abnormal ECG was deemed to be potentially clinically significant.

There were no shifts from normal to clinically significant abnormal in ECG parameters from the placebo and Linacotide 290µg groups. Shifts from baseline to end of Treatment period ECGs are presented in the table below. The overwhelming majority of ECGs were normal at the end of treatment.

Table 43 ECG Shifts from Baseline to End of 12 Week Treatment Period Trial MCP-103-303

Baseline	End of Treatment	Placebo	LIN 133 ug	LIN 266 ug
		(N=209) n / N1 (%)	(N=217) n / N1 (%)	(N=217) n / N1 (%)
Normal	Normal	101/132 (76.5)	118/146 (80.8)	112/137 (81.8)
	Abnormal, NCS	31/132 (23.5)	26/146 (17.8)	25/137 (18.2)
	Abnormal, CS	0/132	2/146 (1.4)	0/137
Abnormal, NCS	Normal	15/ 75 (20.0)	13/ 66 (19.7)	27/ 74 (36.5)
	Abnormal, NCS	60/ 75 (80.0)	53/ 66 (80.3)	47/ 74 (63.5)
	Abnormal, CS	0/ 75	0/ 66	0/ 74
Abnormal, CS	Normal	0/ 0	0/ 0	0/ 0
	Abnormal, NCS	0/ 0	0/ 0	0/ 0
	Abnormal, CS	0/ 0	0/ 0	0/ 0

Source: Table 14.5.6.4A Applicant's Clinical Study Report Trial MCP-103-303 page 1928.
 NCS = Not Clinically Significant CS = Clinically Significant
 Linaclotide 133µg = Linaclotide 145µg Linaclotide 266µg = Linaclotide 290µg.

During the conduct of the trial, there were 6 abnormal ECG findings reported as treatment emergent adverse events. Two of these were cases of atrial fibrillation in the placebo arm. All others occurred in the Linaclotide 145µg arm. Additional details of these can be found in the SAE narratives table above. In addition, there were two SAEs of atrial fibrillation considered Treatment Period SAEs but not, by definition, TEAEs. The following table summarizes abnormal ECG findings reported as TEAE.

Table 44 Abnormal ECG Findings Reported as TEAEs during the conduct of Trial MCP-103-303

Preferred Term	Placebo (N=209)	Linaclotide	
		133 ug (N=217)	266 ug (N=217)
		n (%)	
Atrioventricular block first degree	0	1 (0.5)	0
Sinus arrhythmia	0	1 (0.5)	0
Sinus tachycardia	0	1 (0.5)	0
Ventricular extrasystoles	0	1 (0.5)	0
Atrial fibrillation	2 (1.0)	0 ^a	0

Source: Table 37 Applicant's Clinical Study Report Trial MCP-103-303 page 159
 Patients were counted only once within each SOC and preferred term
 a; There were 2 SAEs of atrial fibrillation considered Treatment Period SAEs, but not by definition TEAEs.

5.3.3.2 Results from Randomized Withdrawal Phase Trial MCP-103-303

By protocol, the safety population during the Randomized-Withdrawal (RW) period was referred to as the RW Analysis Population. The RW Analysis Population consisted of all patients who were re-randomized into the RW period and had ≥ 1 dose of double-blind study drug during the RW period. For the RW period there were 5 treatment sequences.

The disposition of patients participating in the RW period is provided by treatment sequence in the table below. When necessary, “Linaclotide” is abbreviated to “LIN” in this section of the review. In the opinion of this reviewer, it would have been optimal for the applicant to have an additional treatment sequence where patients who were taking placebo during the 12 week Treatment period were re-randomized to the lower dose of Linaclotide 145 μ g during the RW period. It is possible that this group of patients would have also achieved a favorable response to treatment and it would have been preferable to compare the treatment effect achieved with this dose, especially in light of the results from the 12-week Treatment Period. However, this trial was not designed to compare the superiority of one Linaclotide dose over the other. Furthermore the purpose of the RW phase is to determine the durability of treatment response and to determine if rebound (a worsening of symptoms from baseline) or other withdrawal effects occurred after Linaclotide treatment was withdrawn. Therefore the treatment sequences utilized by the applicant are acceptable.

Table 45 Disposition of Patients in the 4 week Randomized Withdrawal Period Trial MCP-103-303

Re-Randomization Sequence During RW Period	LIN 145 μ g \rightarrow LIN 145 μ g	LIN 145 μ g \rightarrow Placebo	LIN 290 μ g \rightarrow LIN 290 μ g	LIN 290 μ g \rightarrow Placebo	Placebo \rightarrow LIN 290 μ g	Totals
Re-Randomized at the end of 12 week Treatment Period	91	95	91	86	177	540
RW Safety Population (RW Analysis)	90	95	90	86	177	538
RW Intent -to-Treat Population	90	95	90	86	177	538
RW Study Completers	89	94	90	85	175	533

Source: Reviewer's table generated from ADL dataset trial MCP-103-303

Overall, there were 540 patients who were re-randomized into the RW period.. Two patients (patient #0213004 in the Linaclotide145 μ g \rightarrow Linaclotide145 μ g sequence and patient #0103011 in the Linaclotide 290 μ g \rightarrow Linaclotide 290 μ g sequence) were re-randomized at the end of the 12 week treatment period but withdrew prior to receiving the first dose of study medication in the RW period. Consequently these patients were not included in the RW Analysis population. Patient #0213004 discontinued for “other reasons”. Patient #0103011 experienced a treatment emergent adverse event that began in the Treatment Period. However the patient was not discontinued from the trial until the RW period. Withdrawal of this patient also occurred prior to receiving the first dose of study medication and therefore this person was included in the safety analysis for the Treatment Period. In addition, there were 5 patients, who did not complete the 4 week RW period. Two patients were discontinued because of protocol violations (patients #0733015 in the Linaclotide

145µg→Linaclotide 145µg treatment sequence and patient #0803008 in the Linaclotide 290µg→placebo treatment sequence). One patient (#0673011) in the placebo→290µg treatment sequence discontinued because of an adverse event. Another patient in the placebo→290µg treatment sequence discontinued for “other reasons”. One patient in the Linaclotide 133µg→placebo sequence (patient #0513010) was lost to follow-up.

The distribution of patients in each treatment sequence and the baseline demographics of patients in each treatment sequence are outlined in the table below. Overall, baseline demographics were fairly consistent between the treatment sequence groups.

Table 46 Baseline Demographics of Patients Entering into the RW Period of Trial MCP-103-303

Characteristic	Re-Randomization Sequence During RW Period of Trial MCP-103-303				
	Linaclotide145µg→ Linaclotide145µg N = 90	Linaclotide145µg → Placebo N = 95	Linaclotide290µg → Linaclotide290µg N = 90	Linaclotide290µg → Placebo N = 86	Placebo→ Linaclotide290µg N = 177
Age (years):					
Mean (standard deviation)	49.5 (13.6)	46.7 (13.5)	46.3 (13.3)	49.4 (14.5)	49.4 (14)
Median	50	46	47	49.5	50
Min, Max	19,82	22,76	18,79	20,83	20,85
Age Group (years) n(%)					
18 < 40:	19 (21.1%)	32 (33.7%)	26 (28.9%)	24 (27.9%)	44 (24.9%)
40 < 65:	59 (65.6%)	51 (53.7%)	57 (63.3%)	48 (55.8%)	111 (62.7%)
≥ 65:	12 (13.3%)	12 (12.6%)	7 (7.8%)	14 (16.3%)	22 (12.4%)
Sex n(%)					
Male	14 (15.6%)	9 (9.5%)	13 (14.4%)	11 (12.8%)	23 (13%)
Female	76 (84.4%)	86 (90.5%)	77 (85.6%)	75 (87.2%)	154 (87%)
Race n(%)					
White (Caucasian)					
Black					
Asian	66 (73.3%)	74 (77.9%)	64 (71.1%)	65 (75.6%)	138 (78%)
American Indian or Alaska Native	22(24.4%)	17 (17.9%)	22 (24.4%)	18 (20.9%)	36 (20.3%)
Native Hawaiian (Other Pacific Islander)	1 (1.1%)	1 (1.1%)	1 (1.1%)	2 (2.3%)	2 (1.1%)
Other	0	1 (1.1%)	0	0	0
Other	0	0	0	1 (1.2%)	0
Other	1 (1.1%)	2 (2.1%)	3 (3.3%)	0	1 (0.6%)
Ethnicity n(%)					
Not Hispanic/Latino	82 (91.1%)	91 (95.8%)	80 (88.9%)	82 (95.3%)	171 (96.6%)
Hispanic/Latino	8 (8.9%)	4 (4.2%)	10 (11.1%)	4 (4.7%)	6 (3.4%)
Body Mass Index					
Mean (standard deviation)	27.9 (6.9)	28 (6.5)	27.6 (5.6)	27.6 (5.6)	27.7 (5.6)
Median	26.7	26.8	26.7	26.7	27.1
Min, Max	15.1, 69.9	18.7, 48.5	19.8	19.9, 48.6	18.2, 50.4

Source: Reviewer’s Table Generated from ADSL dataset MCP-103-303

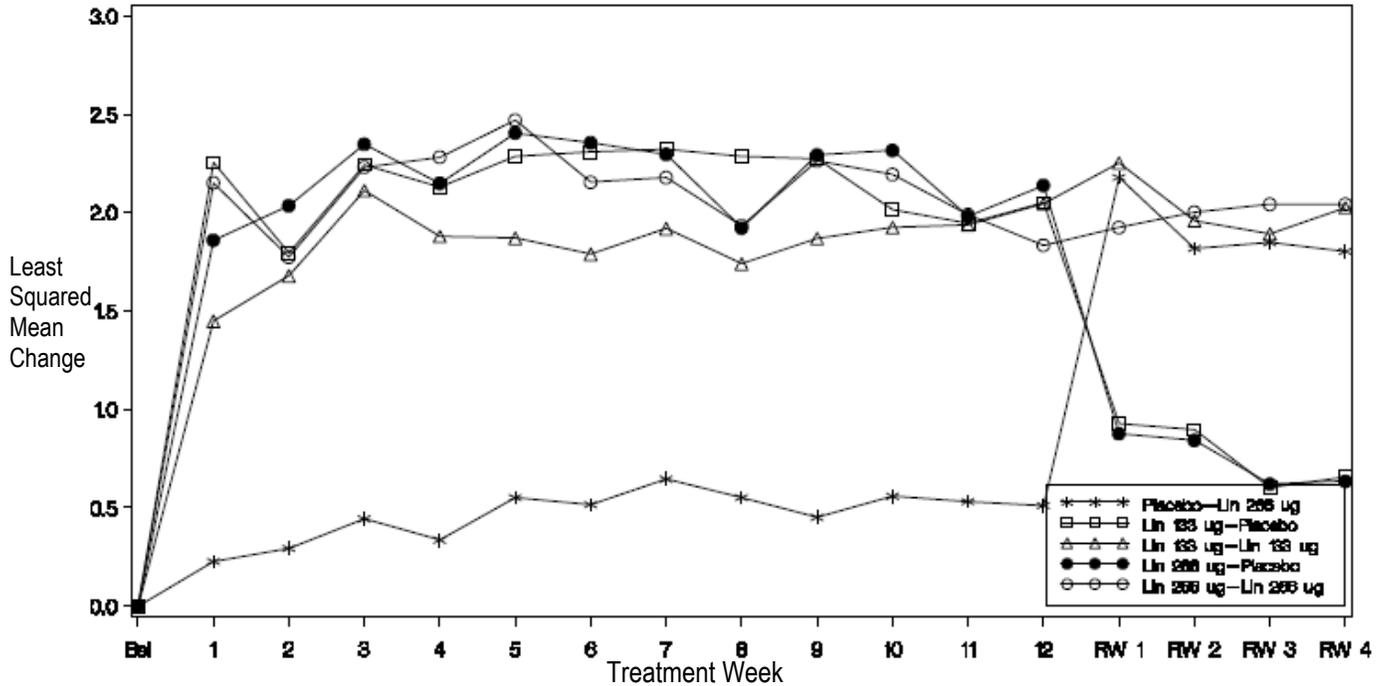
Over 80% of patients in each of the treatment sequences reported concomitant medication use. The concomitant medications used by patients during the RW period were similar to those used during the Treatment period.

The percentage of patients who were $\geq 80\%$ IVRS compliant during the RW Period was 74% for the Placebo→Linaclotide 290 μ g Treatment Sequence; 74% for the Linaclotide 145 μ g →Placebo Treatment Sequence; 79% for the Linaclotide 145 μ g→Linaclotide 145 μ g Treatment Sequence; 73% for the Linaclotide 290 μ g → Placebo Treatment Sequence; and 67% for the Linaclotide 290 μ g → Linaclotide 290 μ g Treatment Sequence. The overall treatment compliance was at least 97% for all Treatment Sequences during the RW period.

For the RW Period, descriptive statistics and confidence intervals were presented by Treatment Sequence as change from baseline for the following parameters: CSBM weekly frequency; SBM weekly frequency; Stool consistency as measured by Bristol Stool Form Scale; Severity of Straining as measured by the Ease of Passage Scale; Abdominal Discomfort, Bloating, Constipation Severity, and percentage of days of using per-protocol rescue medicine or any other laxative, suppository, or enema. In the opinion of this reviewer, “Severity of Straining,” “Abdominal Discomfort”, “Bloating”, and “Constipation Severity” are subjective in nature and difficult to interpret.

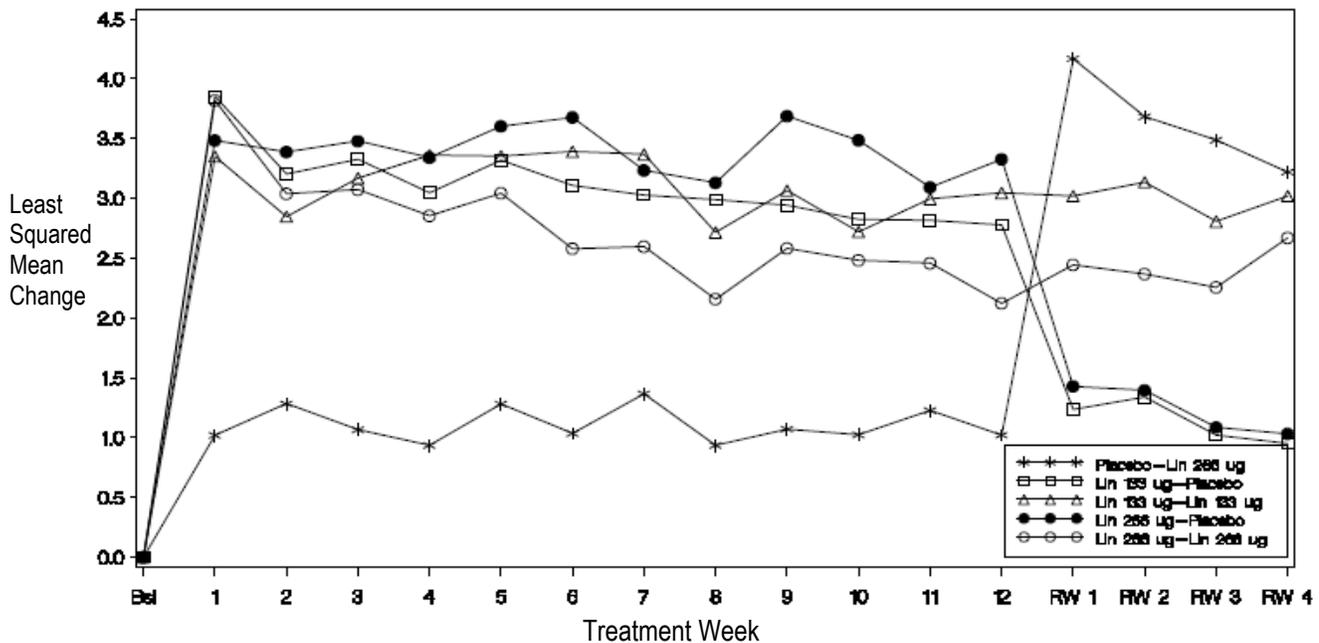
Change from Baseline in CSBM and SBM weekly frequency rates are provided in the graphic below reproduced from the Applicant’s submission. (Note: Linaclotide 133 μ g corresponds to Linaclotide 145 μ g. Linaclotide 266 μ g corresponds to Linaclotide 290 μ g.) For those patients being treated with either the 145 μ g or 290 μ g Linaclotide dose at baseline during the 12 week Treatment Period, the CSBM and SBM frequency rates were maintained if they stayed on Linaclotide. However, for those patients who were re-randomized to placebo following treatment with either the 145 μ g or 290 μ g Linaclotide dose during the initial 12 weeks, both the CSBM and SBM frequency rates decreased during the RW period to rates similar to those seen in placebo-treated patients during the Treatment Period. Mean changes in CSBM and SBM frequency rates from baseline in patients initially treated with placebo and re-randomized to 290 μ g Linaclotide during the RW period, increased to levels in the group of patients treated with 290 μ g of Linaclotide during the Treatment Period.

Figure 10 Change from Baseline in CSBM Weekly Frequency Rate Randomized Withdrawal Analysis Population



Source: Applicant's Figure 14.4.2B p1995 Clinical Study Report MCP-103-303

Figure 11 Change from Baseline in SBM Weekly Frequency Rate - RW Analysis Population Trial MCP-103-303



Source: Applicants Figure 14.4 2.2B p1997 Clinical Study Report Trial MCP-103-303

Mean changes from Baseline in Stool Consistency (as measured by the Bristol Stool Form Scale) are presented in the Table below. (Please See Appendix for Graphic of Bristol Stool Form Scale). Lower scores would indicate a harder stool consistency suggesting a higher degree of constipation. A numerically larger change from baseline would indicate a greater improvement (i.e. softening of stools) from baseline in stool consistency.

Table 47 Summary of Mean Change from Baseline in Stool Consistency as Measured by Bristol Stool Form Scale During RW Period Trial MCP 103-303

Parameter	Re-Randomization Sequence During RW Period of Trial MCP-103-303				
	LIN 145µg → LIN145µg N = 90	LIN 145µg → Placebo N = 95	LIN 290µg → LIN 290µg N = 90	LIN 290µg → Placebo N = 86	Placebo → LIN 290µg N = 177
Bristol Stool Form Scale	1.943 (1.628, 2.259)	0.966 (0.707, 1.224)	1.609 (1.289, 1.928)	0.802 (0.502, 1.101)	1.882 (1.630, 2.134)

Source: Reviewer's Table: Modified from Table 25 Clinical Study Report Trial MCP-103-303

The change from baseline in the Percentage of Days of Rescue Medication use was also assessed for the Randomized Withdrawal periods. That data is presented in the table below. All Treatment Sequences had a decrease for this parameter. The mean change from baseline was greatest for the Placebo → Linaclotide 290 µg Treatment Sequence (-7.078), and smallest for the Linaclotide 145µg → Placebo Treatment Sequence (-0.589). The fact that all Treatment sequences decreased for this parameter is somewhat confusing as one would have anticipated that the Percentage of Days of Rescue Medication use in patients re-randomized to placebo during the RW Period would have increased rather than decreased. This would have been consistent with the decrease in CSBM and SBM weekly frequency rates observed for those treatment sequences. The fact that no increase in Rescue Medication use was observed may be artifact, it may reflect bias, or it may reflect the fact that there was no wash-out period between the Treatment and RW period. It is possible that the use of rescue medication in the group of patient re-randomized to placebo would increase over time. However, there are no data to support this hypothesis.

Table 48 Change from Baseline in Percentage of Days of Rescue Medication Use During the RW Period Trial MCP 103-303

Change from baseline in percentage of days of	Re-Randomization Sequence During RW Period of Trial MCP-103-303				
	Linaclotide145µg → Linaclotide145µg N = 90	Linaclotide145µg → Placebo N = 95	Linaclotide290µg → Linaclotide290µg N = 90	Linaclotide290µg → Placebo N = 86	Placebo → Linaclotide290µg N = 177
Mean Change from baseline	-3.933 (16.71)	-0.589 (19.29)	-1.169 (22.69)	-2.515 (24.65)	-7.078 (16.60)
(95% CI)	(-7.432, -0.435)	(-4.518, 3.341)	(-5.922, 3.584)	(-7.800, 2.770)	(-9.540, -4.616)

Source: Reviewer's Table with Modifications from Applicant's Clinical Study Report Tables 14.4.3.15D

An overview of the Adverse Events occurring during the RW period is provided in the table below. Patients initially taking placebo followed by re-randomization to Linaclotide 290µg experienced the highest percentage of TEAEs (26%). More patients in the "Placebo → Linaclotide 290µg" sequence also experienced Treatment Related Adverse Events. Most of

these AEs were from the Gastrointestinal SOC and the most commonly reported TEAE was diarrhea.

Two patients in the Linaclotide 145µg → Placebo treatment sequence experienced a serious AE. One patient in the Placebo → Linaclotide 290µg treatment sequence discontinued due to an adverse event. An overview is provided in the tables below.

**Table 49 Overview of Patients Experiencing Adverse Events during RW period by Treatment Sequence
 RW Analysis Population Trial MCP-103-303**

	Re-Randomization Sequence During RW Period of Trial MCP-103-303				
	Linaclotide145µg→ Linaclotide145µg N = 90	Linaclotide145µg → Placebo N = 95	Linaclotide290µg → Linaclotide290µg N = 90	Linaclotide290µg → Placebo N = 86	Placebo→ Linaclotide290µg N = 177
Total Number of Patients Experiencing an AE by Treatment Arm (TEAE)	20 (22.2%)	18 (18.9%)	18 (20.0%)	15 (17.4%)	46 (26.0%)
Number of Patients Experiencing at least 1 Treatment RELATED Adverse	3 (3.3%)	3 (3.2%)	2 (2.2%)	4 (4.7%)	23 (13%)
Number of Patients Experiencing Each Category of Adverse Events					
Death	0	0	0	0	0
Serious Adverse Event (SAE)	0	2 (2.1%)	0	0	0
AE Resulting in Early Withdrawal	0	0	0	0	1 (0.6%)

Source: Reviewer's Table

Table 50 Overview of Adverse Events During RW Period Trial MCP-103-303 RW Analysis Population

	Re-Randomization Sequence During RW Period of Trial MCP-103-303				
	Linaclotide145µg → Linaclotide145µg N = 90	Linaclotide145µg → Placebo N = 95	Linaclotide290µg → Linaclotide290µg N = 90	Linaclotide290µg → Placebo N = 86	Placebo → Linaclotide290µg N = 177
Total Number of Patients Experiencing an AE by	20 (22.2%)	18 (18.9%)	18 (20.0%)	15 (17.4%)	46 (26.0%)
Total Number of TEAE by Treatment Sequence	36	42	44	31	72
Category of Adverse Events					
Events that resulted in Death	0	0	0	0	0
Events that were considered SAEs	0	2 (4.8%)	0	0	0
Events leading to Treatment Discontinuation	0	0	0	0	1 (1.4%)
Events leading to Interruption of Trial Treatment Therapy	0	0	12	0	6

Source: Reviewer's Table Generated from ADAE dataset Trial MCP 103-303

The highest number of adverse events occurred in patients re-randomized to Linaclotide 290µg following treatment with placebo. The most commonly occurring adverse event experienced by this group was diarrhea which accounted for over 30% of the TEAEs in each treatment sequence with the exception of the Linaclotide145µg → placebo treatment sequence where diarrhea accounted for 18% of the TEAEs. This is not surprising as you would expect patients on placebo to experience less diarrhea than those on study drug treatment. Overall the incidences of treatment emergent adverse events were similar across the other 4 Treatment sequences and consistent with what was seen during the 12 weeks of the Treatment period

In order to compare the incidence of TEAEs in the 4-week RW period to the incidence of TEAEs in the Treatment Period, the applicant provided a summary comparing the TEAEs in the RW period with the first 4 weeks of the Treatment period. Diarrhea was experienced with a higher incidence by placebo-treated patients during the first 4 weeks of the Treatment period compared to patients re-randomized to placebo during the RW period. This may be related to reporting bias that developed in patients over the trial period. A similar pattern was observed in patients treated with Linaclotide during the first 4 weeks of Treatment experienced a higher incidence of flatulence, nausea, and abdominal pain than those re-randomized to Linaclotide following initial treatment with Placebo. Such trends may be indicative of decreased reporting of adverse events over time. This hypothesis may also be supported by the fact that for those patients taking Linaclotide who were re-randomized to the same dose of Linaclotide during the RW period reported less diarrhea than during the first 4

weeks of treatment.) The incidence of diarrhea was similar between patients treated with Linaclotide during the first 4 weeks of the Treatment Period and patients re-randomized to 290µg Linaclotide in the RW period following treatment with placebo in the Treatment Period.

The incidence of newly emergent AEs was consistent with the incidence of TEAEs in the RW Period and similar across 4 of the 5 treatment sequences. Again, the highest percentage of patients experiencing a newly emergent AE (25.4%) were those in the Placebo → Linaclotide 290µg group Treatment Sequence.

Table 51 Incidence of Newly Emergent Adverse Events during RW period of Trial MCP-103-303 RW Analysis Population

Preferred Term	RW: Placebo		RW: Linaclotide		
	133 ug - Placebo (N=95)	266 ug - Placebo (N=86)	133 ug - 133 ug (N=90)	266 ug - 266 ug (N=90)	Placebo - 266 ug (N=177)
	n (%)				
Patients with at least 1 NEAE	16 (16.8)	15 (17.4)	20 (22.2)	16 (17.8)	45 (25.4)
Urinary tract infection	0	1 (1.2)	2 (2.2)	4 (4.4)	3 (1.7)
Diarrhea	1 (1.1)	0	2 (2.2)	1 (1.1)	20 (11.3)
Nausea	3 (3.2)	0	0	1 (1.1)	1 (0.6)
Abdominal pain	2 (2.1)	3 (3.5)	0	0	0

Source: Applicants Table 42 Clinical Study Report Trial MCP-103-303 verified by Clinical Reviewer

The incidence of related TEAEs were similar across four of the Treatment sequences: 3.2% in the Linaclotide 145µg → Placebo sequence; 3.3% in the Linaclotide 145µg → Linaclotide 145µg sequence; 4.7% in the Linaclotide 290µg → Placebo sequence; 2.2% in the Linaclotide 290µg → Linaclotide 290µg sequence. Again, patients re-randomized to Linaclotide 290µg following treatment with placebo experienced the highest incidence of treatment related adverse events (13%) The majority of TEAEs were mild to moderate in severity.

Only one patient (#0673011) withdrew during the RW period. This patient, an 82 year old Asian male, was re-randomized from Placebo to 290µg of Linaclotide. The patient's past medical history was significant for diabetes, hiatal hernia, hemorrhoids, and depression. Concomitant medications included docusate and psyllium for constipation and simethicone for stomach gas. Three days after starting Linaclotide the patient reported severe abdominal discomfort. Study drug treatment was held and the patient's symptoms resolved one day after onset. When the patient resumed study drug treatment, his abdominal discomfort returned. Per protocol, the patient was discontinued from the trial and the event was assessed as probably related to study drug treatment.

There were no deaths during the RW period. Two patients experienced a serious adverse event during the RW period. A summary of SAEs is provided in the table below.

Table 52 Descriptive Summaries of Serious Adverse Events during Randomized-Withdrawal (RW) period of Trial MCP-103-301 Safety Population

Subject Number	Treatment Sequence	Exact Term Reported for the SAE	MedDRA preferred Term for SAE	Number of Days to SAE Start	Narrative	AE Severity	Investigator Assessment of Relatedness	Reviewer Assessment of Relatedness
0093022	Linacotide 145µg → Placebo	Atrial fibrillation with rapid ventricular response	Atrial Fibrillation		68year old White male with past medical history of chronic constipation, colon polyps, gastritis, GERD, backpain, benign prostatic hypertrophy, bipolar disorder, depression, sleep disturbance, drug allergy, ventricular tachycardia, hypercholesterolemia, chest pain. Patient had a cardiac catheterization several years prior to study start and surgeries for pain and upper extremity injuries. Concomitant medications included aspirin, diazepam, lorazepam, sucralfate, tamsulosin (for BPH), tranylcypromine, On RW trial Day 14, patient had diarrhea and abdominal distension which lasted 1 day. On RW trial Day 18 the patient had chest pain, worsening dizziness, nausea, vomiting, dyspnea, and hyperhidrosis. The symptoms persisted for (b) (6) until RW trial (b) (6) when the patient was advised to go to the hospital. While in the hospital observation unit, the patient reported palpitations and numbness in his bilateral upper and lower extremities. ECGs showed atrial fibrillation with rapid ventricular response and sinus bradycardia. (NOTE: By definition patients with atrial fibrillation are tachycardic.) Chest Xray and CT were normal. Echocardiogram and laboratory assessments were not provided. The patient was treated with warfarin, diltiazem, methylprednisolone, famotidine, prednisone, and enoxaparin and was released from hospital observation. The atrial fibrillation and all of the patient's symptoms were reported resolved on RW trial Day 26 (8 days after they began). The patient remained on study drug without interruption and was able to complete the trial. Triplicate ECGs at the termination visit were not clinically significant.	Mild	Unrelated	Unrelated

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Subject Number	Treatment Sequence	Exact Term Reported for the SAE	MedDRA preferred Term for SAE	Number of Days to SAE Start	Narrative	AE Severity	Investigator Assessment of Relatedness	Reviewer assessment of Relatedness
1103005	Linacotide 145µg → Placebo	Pulmonary embolism	Pulmonary Embolism		72 year old White female with a past medical history of chronic constipation, GERD, chest pain, osteoporosis, hypertension, hyperlipidemia, coronary artery disease (s/p myocardial infarction) left bundle branch block, allergies, hemorrhoids, gallstones. Patient experienced a stroke prior to enrolling in the trial. Concomitant medications included Nexium, Boniva for osteoporosis, Ecotrin, Vitamin C, Singulair, Altace for hypertension, Crestor. During the Treatment period the patient was treated for a community acquired pneumonia. The patient was able to continue study drug without interruption and completed the treatment phase of trial MCP-103-303 prior to being re-randomized in the RW period. (Please see the table of SAFs for the Treatment Period of Trial MCP-103-303). On RW trial (b) (6), the patient fell and hurt her knee. A chest Xray during hospitalization for that injury preliminarily showed cardiomegaly. On RW trial Day 21 (26 days after the pneumonia had reportedly resolved), the patient developed chest pain and shortness of breath. She was diagnosed with a pulmonary embolism. However, it is not exactly clear how this diagnosis was established. Bilateral venous Doppler ultrasound of the lower extremities showed no evidence of a clot. Chest Xray showed no evidence of fracture, pleural effusion, or pneumothorax. The patient was treated with famotidine for reflux, with glyceryl trinitrate for chest pain, with paracetamol for pain, and with heparin and warfarin for the (b) (6) pulmonary embolism. The patient remained in the hospital for (b) (6). The event was considered resolved by RW trial (b) (6) when the patient was discharged. Discharge INR was 2.4. Discharge medications included warfarin and Tylenol. During the event, the patient was able to continue study drug treatment uninterrupted. The patient completed the trial.	Severe	Unrelated	Unrelated

Source: Reviewer's Table generated using ADAE dataset for Trial MCP 103-303 and patient case report forms and narratives submitted by the Applicant.

Like the treatment period, there were no clinically meaning trends in laboratory assessments over the RW period. Two patients in each of the 290 Linaclotide→ Placebo; Linaclotide 145µg → Linaclotide 145µg; Linaclotide 145µg → Linaclotide 290µg treatment sequences experienced an abnormal laboratory treatment emergent AE.

There were no trends in changes from baseline of vital signs considered to be clinically meaningful. One patient in the Placebo→ Linaclotide 290ug Treatment Sequence (patient #0633017) experienced a TEAE of increased systolic blood pressure considered moderate in severity and unrelated to study drug. However, this event did not meet pre-specified criterion for potentially clinically significant increased blood pressure (SBP \geq 180 and increase by \geq 20)

Overall there were no significant trends in ECG changes. One patient in the Linaclotide 145µg → placebo treatment sequence who had an abnormal ECG at baseline that was not considered clinically significant ended the RW period with an ECG that was abnormal and clinically significant. All other potentially clinically significant ECG changes (4 patients/events) occurred in the Placebo → 290µg Treatment sequence. Like the Treatment Period, a subset of patients in the RW period had triplicate ECGs performed. According to the applicant, for this subset of patients, an average of the 3 consecutive ECG values for each measurement at each visit was used to generate summary statistics. Measurements were recorded for PR interval, QRS duration, RR interval, QT interval, RR interval, QTc interval Bazett, and QTc interval Fridericia. Overall the mean changes in each ECG parameter after dosing with study drug were not clinically meaningful. One patient (# 0093023) in the triplicate ECG cohort had an individual QTc value of > 500 during the RW Period. Patient 0093023 was in the in the Placebo → Linaclotide 290µg Treatment Sequence and had QTc intervals (Bazett) of 502 and 512 msec and a QTc interval (Fridericia) of 503 msec at the RW Day 29 visit. (Baseline values were 482.3 [Bazett] and 474.0 [Fridericia]). Two patients had abnormal ECGs reported as TEAEs. Both patients were in the Linaclotide 145µg → Placebo Treatment Sequence. One patient (#0753003) had an unrelated inverted T-wave on ECG during the RW Period and the other had atrial fibrillation.

6 Review of Efficacy

Efficacy Summary

Linaclotide is being developed for the treatment of chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C). In support of the CIC indication, the applicant submitted two phase 3 trials. Trial LIN-MD-01 (hereafter also referred to as LIN-01) was a 12-week Multi-center, Randomized, Double-blind, Placebo-Controlled, Parallel-Group trial comparing two doses of Linaclotide (145µg and 290µg) with placebo in patients diagnosed with CIC using modified Rome II criteria for functional constipation. Trial MCP-101-303 (hereafter also referred to as MCP-303) was a 16-week Multi-center, Randomized, Double-blind, Placebo-Controlled, Parallel-Group trial comparing two doses of Linaclotide with placebo in patients diagnosed with CC using modified Rome II criteria. Treatment was administered for 12 weeks in Trial MCP-103-303, followed by a 4-week Randomized Withdrawal (RW) period. This was the only difference in the design of the two trials.

The primary endpoint for both trials was “12-week complete spontaneous bowel movement (CSBM) Overall Responder.” The primary endpoint is consistent with the Division’s prior requirements for this indication. A CSBM Overall Responder was defined as a patient who was a CSBM Weekly Responder (defined as having CSBM ≥ 3 with an increase from baseline of ≥ 1 for the week) for at least 9 weeks of the 12 weeks of treatment. For each of the two Linaclotide dose groups, the proportion of 12-week CSBM overall responders were compared to the proportion of 12-week CSBM overall responders in the placebo group using the Cochran-Mantel-Haenszel (CMH) test. The absolute number and percentage of 12-week CSBM Overall Responders for each of the Linaclotide treatment groups; the difference in responder rate between each Linaclotide group and placebo-group; the Cochran-Mantel-Haenszel estimates of odd ratios with corresponding confidence intervals; and the two-sided p-values associated with the CMH test were presented. Please refer to the statistical review for additional details.

The initial determination of a patient being a 12-week CSBM Overall Responder or CSBM Weekly Responder did not incorporate IVRS call compliance. Therefore a patient that had less than 4 IVRS responses could potentially be treated as a responder. However if a patient prematurely discontinued from the trial such that the patient’s final Treatment Period week contained less than 4 days, the patient was not considered a CSBM Weekly Responder for that week or the subsequent missed weeks of the Treatment Period. Following an information request, the applicant performed a sensitivity analysis of the primary efficacy endpoint where a study participant with less than 4 complete IVRS calls in a Treatment Period week was considered a nonresponder for that week. The primary endpoint (12 week CSBM overall responder) was then recalculated based on the new modified CSBM Weekly Responder endpoints.

The following tables present the primary efficacy results (using the modified CSBM responder definition) for each of the pivotal trials at the end of the 12-week treatment periods. For both

of the double-blind placebo-controlled Phase 3 trials, the percentage of overall CSBM responders was greater in both doses of the Linaclotide arms relative to the placebo arms.

The trials were not designed to assess the superiority (or noninferiority) of one dose of Linaclotide over the other. For the primary efficacy variable (CSBM overall responder), the 290µg dose had a larger treatment effect over placebo than the 145µg dose in trial LIN-MD-01 (14.7% and 9.9%) respectively. However, in Trial MCP-103-303, the Linaclotide 145µg dose had a larger treatment effect over placebo than the Linaclotide 290µg dose (17.0% and 15.7% respectively). (Please refer to the table below.) The Linaclotide 290µg dose does not appear to confer any additional benefit than the 145 µg group. Subgroup analyses failed to identify any population in which the 290µg dose consistently offered additional clinically meaningful benefit over the 145µg dose.

Table 53 Summary of Primary Efficacy Results for Pivotal CIC Trials – (Modified ITT Population[±])

	Trial LIN-MD-01			Trial MCP-103-303		
	Placebo	Linaclotide 145µg	Linaclotide 290µg	Placebo	Linaclotide 145µg	Linaclotide 290µg
CSBM Overall Responder	12/215 (5.6%)	33/213 (15.5%)	41/202 (20.5%)	7/209 (3.3%)	44/217 (20.3%)	41/216 (19.0%)
Nonresponder	203 (94.4%)	180/213 (84.5%)	161/202 (79.7%)	202/209 (96.7%)	173/209 (79.7%)	175/216 (81.0%)
Difference (95% Confidence Interval)		9.9% (3.7%, 16.1%)	14.7% (8.1%, 21.7%)		17.0% (10.6%, 23.3%)	15.7% (9.7%, 22.3%)
P-value		0.002	<0.001		<0.001	<0.001

Source: Modified from Statistical Reviewer's Midcycle Slides dated January 18, 2012.

± For this Modified Table: A 12 week-CSBM overall responder is a patient who is 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, increased by 1 or more from baseline and who completed at least 4 IVRS calls for that week

In addition to the primary endpoint, the applicant also included the following pre-specified key secondary endpoints and a number of "additional" endpoints: .

- Change from baseline in 12-week CSBM frequency rate,
- Change from baseline in 12-week SBM frequency
- Change from baseline in 12-week Stool consistency
- Change from baseline in 12-week Severity of Straining
- Change from baseline in Abdominal Discomfort
- Change from baseline in Bloating
- Change from baseline in Constipation Severity

The following sections present more detailed information on the integrated efficacy results for the trials submitted in support of the chronic idiopathic constipation indication..

6.1 Indication

The applicant is seeking two indications for this application:

- The treatment of irritable bowel syndrome with constipation
- The treatment of chronic constipation.

There are two doses proposed for use in the treatment of chronic constipation (145 µg and 290 µg). One dose was proposed for the treatment of irritable bowel syndrome with constipation (290 µg). This efficacy review will focus on the two Phase 3 trials submitted in support of the treatment of chronic constipation indication. Please refer to the review of Dr. Lara Dimick-Santos for additional information regarding the treatment of irritable bowel syndrome with constipation indication and information regarding the long-term safety trials.

Chronic constipation may have a number of underlying etiologies including drug, gastroparesis, or biochemical or underlying anatomical defects. The applicant enrolled patients into the pivotal trials using modified Rome II criteria for functional constipation, which by definition has no known etiology. Therefore the efficacy evaluation will focus on the acceptability of the applicant's data for the treatment of the signs and symptoms of chronic idiopathic constipation.

6.1.1 Methods

The reader should refer to Section 5.3 for more information. The core of the clinical development program for Linaclotide use in patients with chronic idiopathic constipation includes 2 pivotal Phase 3 trials to assess safety and efficacy. A total of 1275 patient with chronic idiopathic constipation were evaluated in the pivotal trial. A general description of the design of each of the Phase 3 double-blind trials is provided in Section 5.3. Trial LIN-MD-01 was a 12-week Phase 3 Randomized, Double-Blind Placebo Controlled Trial to assess the safety and efficacy of two doses of Linaclotide (145µg and 290µg) for the treatment of chronic constipation. The trial was conducted across 95 centers in the United States (U.S.) and 8 centers in Canada. Trial MCP-103-303 was a 16 week Double-Blind, Placebo-Controlled, Randomized-Withdrawal Trial identical in design to Trial LIN-MD-01. Trial MCP-103-303 also contained a 4 week Randomized Withdrawal period. Trial MCP-103-303 was conducted across 103 centers in the U.S. All trials submitted in support of the chronic constipation indication are found in the Table in Section 5.1. There were also two Phase 2 supportive trials conducted in 352 chronic idiopathic constipation patients. The Phase 2 trials evaluated the safety and efficacy of Linaclotide across a range of Linaclotide doses prior to the final selection of the 145µg and 290µg doses. Finally, there were two long-term safety trials (each 78 weeks in duration) submitted in support of the chronic idiopathic constipation indication. Those trials were evaluated by Dr. Lara Dimick Santos.

Throughout the Phase 3 trials, Linaclotide was administered orally once a day and 30 minutes prior to the first meal of the day. A placebo treatment arm was selected in order to provide comparable treatment groups and minimize the potential for selection or investigator bias. Patients were enrolled using Modified Rome II criteria for functional constipation.

Treatment outcomes for the chronic idiopathic constipation trials were measured using patient reports of symptoms. The selection of the Phase 3 primary efficacy and secondary efficacy parameters was based on historical precedent of outcome measures from drugs previously approved for the indication; a review of the published literature; qualitative research in patients with chronic idiopathic constipation, expert input, and the results of the Phase 2b trials. An overall CSBM responder analysis was chosen for the primary endpoint for the pivotal Phase 3 trials. In addition, the pharmacodynamics of orally administered Linaclotide across the clinical development program was evaluated through bowel symptom assessments of stool consistency (using the Bristol Stool Form Scale [BSFS]), severity of straining (using the seven-point Ease of Passage Scale or a five-point severity of straining scale), stool frequency, and stool weight. The BSFS score used to determine stool consistency enabled patients to classify the form or consistency of their stool into one of seven categories, ranging from hard (Type 1) to entirely liquid (Type 7), with Types 3-4 representing the normal form. Because the form of the feces largely depends on the time spent in the colon (i.e., slower transit results in harder stool form), measuring stool consistency using the BSFS was considered by the applicant to be a surrogate for GI transit.

The plan was to enroll 600 patients in each of the pivotal clinical trials. To be included in the intent-to-treat population, a study enrollee had to have taken at least 1 dose of study drug treatment and have had at least 1 post-baseline assessment. The primary endpoint was analyzed using a Cochran-Mantel-Haenszel (CMH) test. Secondary endpoints were analyzed using an analysis of covariance (ANCOVA). The applicant adjusted for multiplicity using the Hochberg technique.

6.1.2 Demographics

Please refer to sections 5.3 and 7.2.1 for additional details. Both of the pivotal trials enrolled a majority of Caucasian, female, non-Hispanic patients with chronic idiopathic constipation. Of the Linaclotide treated patients, approximately 88% were under the age of 65 years, approximately 89% were female, 76% were white, and 90% were non-Hispanic. The median age of enrollees was approximately 48 years. Approximately a third of patients were obese (BMI $\geq 30\text{kg/m}^2$). Baseline demographics were equally distributed across the treatment arms of the Phase 3 placebo-controlled double blind trials. A summary of the race, gender and mean ages of patients in the Phase 3 placebo controlled trials is provided in the table below. This is followed by a table of the pooled demographic and baseline characteristics for the pivotal Phase 3 trials.

Table 54 Race, Gender, and Mean Age of Chronic idiopathic constipation Patients in Phase 3 Double-Blind Placebo Controlled Trials (MCP-103-303 and LIN-MD-01) ITT Population

Demographic Characteristic	MCP-103-303			LIN-MD-01		
	Placebo N = 209	Linaclotide		Placebo N = 215	Linaclotide	
		145 ug N = 217	290 ug N = 216		145 ug N = 213	290 ug N = 202
Race						
Caucasian n(%)	160 (77)	164 (76)	157 (73)	168 (78)	168 (79)	152 (75)
Black n(%)	46 (22)	46 (21)	52 (24)	42 (20)	41 (19)	46 (23)
Other n(%)	3 (1)	7 (3)	7 (3)	5 (2)	4 (2)	4 (2)
Gender						
Male n(%)	27 (13)	26 (12)	28 (13)	19 (9)	18 (9)	23 (11)
Female n(%)	182 (87)	191 (88)	188 (87)	196 (91)	195 (92)	179 (89)
Age						
Mean	49	47	48	47	49	47
≥ 65 n(%)	28 (13)	27 (12)	27 (13)	27 (13)	24 (11)	21 (10)

Source: Adapted from Table 3.1.2.1-1 Applicant's integrated Summary of efficacy page 53.

Table 55 Demographic and Baseline Characteristics Pooled Phase 3 Placebo-Controlled Double Blind Trials in Support of Chronic idiopathic constipation Indication

Demographic Characteristic	Placebo (N = 423)	Linaclotide		Total (N = 1271)
		145 µg (N = 430)	290 µg (N = 418)	
Age, years				
Mean (SD)	48.2 (13.9)	47.8 (13.3)	47.5 (13.7)	47.8 (13.6)
Median (Min, Max)	48.0 (18, 85)	48.0 (19, 83)	47.0 (18, 83)	48.0 (18, 85)
Age, n (%)				
< 65	368 (87.0)	379 (88.1)	370 (88.5)	1117 (87.9)
65 to < 75	44 (10.4)	41 (9.5)	39 (9.3)	124 (9.8)
≥ 75	11 (2.6)	10 (2.3)	9 (2.2)	30 (2.4)
Gender, n (%)				
Female	377 (89.1)	386 (89.8)	367 (87.8)	1130 (88.9)
Male	46 (10.9)	44 (10.2)	51 (12.2)	141 (11.1)
Race, n (%)				
Black	88 (20.8)	87 (20.2)	98 (23.4)	273 (21.5)
Caucasian	327 (77.3)	332 (77.2)	309 (73.9)	969 (76.2)
Other	8 (1.9)	11 (2.6)	11 (2.6)	30 (2.4)
Ethnicity, n (%)				
Hispanic/Latino	36 (8.5)	42 (9.8)	49 (11.7)	127 (10.0)
Not	387 (91.5)	388 (90.2)	369 (88.3)	1144 (90.0)
Height, cm				
Mean (SD)	165.0 (8.3)	164.8 (8.1)	165.3 (8.6)	165.1 (8.3)
Median (Min, Max)	165.1 (134.6, 203.2)	164.8 (133.4, 190.5)	165.0 (137.2, 195.6)	165.0 (133.4, 203.2)
Weight, kg				
Mean (SD)	77.1 (18.2)	75.8 (17.2)	75.8 (16.4)	76.2 (17.3)
Median (Min, Max)	75.4 (45.5, 167.8)	72.9 (44.0, 179.5)	74.0 (46.4, 158.8)	74.0 (44.0, 179.5)
BMI, kg/m²				
Mean (SD)	28.3 (6.4)	27.9 (5.9)	27.7 (5.5)	28.0 (6.0)
Median (Min, Max)	27.3 (17.9, 72.3)	26.9 (15.1, 69.9)	27.2 (16.8, 53.6)	27.2 (15.1, 72.3)

Source: Table 3.1.2.2-1 Applicant's Integrated Summary of Efficacy page 55.

6.1.3 Subject Disposition

Additional information may be found in Section 7.3. A total of 1275 patients were enrolled in the trials. Of these 1271 were included in the ITT population. Approximately 84% of patients treated with Linaclotide completed the trial compared to 87% of patients in the placebo arm. The following table contains the patient disposition of the pooled phase 3 pivotal chronic idiopathic constipation trials.

Table 56 Chronic idiopathic constipation Patient Disposition Pooled Phase 3 Placebo-Controlled Double-Blind Trials (LIN-MD-01 and MCP-103-303)

	Placebo (N = 423) n (%)	Linaclotide		Total (N = 1275) n (%)
		145 µg (N = 430) n (%)	290 µg (N = 422) n (%)	
Completed Treatment Period ^a	367 (86.8)	358 (83.3)	345 (81.8)	1070 (83.9)
Prematurely Discontinued	56 (13.2)	72 (16.7)	77 (18.2)	205 (16.1)
Reason for Premature Discontinuation				
Adverse Event	18 (4.3)	32 (7.4)	31 (7.3)	81 (6.4)
Protocol Violation	8 (1.9)	5 (1.2)	7 (1.7)	20 (1.6)
Withdrawal of Consent	10 (2.4)	18 (4.2)	18 (4.3)	46 (3.6)
Lost to Follow-up	4 (0.9)	13 (3.0) ^b	16 (3.8) ^b	33 (2.6)
Insufficient Therapeutic Response	12 (2.8)	1 (0.2)	3 (0.7)	16 (1.3)
Other Reasons	4 (0.9)	3 (0.7)	2 (0.5)	9 (0.7)

Source: Table 3.1.3.2-1 Applicant Integrated Summary of Efficacy page 58.

N = Number of patients in that Treatment Arm

n = Number of patients within each specific category

a: Patients who stayed on on-study through Visit 7 (Week 12) and then were re-randomized for entry into the Randomized-Withdrawal Period are counted as completing treatment.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy variable was “12-week CSBM overall responder during the 12 weeks of the treatment period.” A “12-week CSBM Overall Responder” was defined as 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. Per protocol, a complete spontaneous bowel movement (CSBM) was defined as a SBM that was associated with a sense of complete evacuation. A spontaneous bowel movement (SBM) was defined as a bowel movement that occurred in the absence of laxative, enema, or suppository use on either the calendar day of the bowel movement or the calendar day before the bowel movement.

The 12 week duration is acceptable for the study of treatments used in chronic conditions. “Prior studies that investigated medical treatments for chronic idiopathic constipation, have utilized the following primary outcomes: frequency rate of SBM during a specified time frame; proportion of subjects with weekly rescue free bowel movement rate ≥ 3 ; occurrence of a bowel movement within 8 hours following daily administration of study medication; change in average weekly SBM frequency at week 3; and CSBM overall responder defined as a subject who meets the criteria of being a CSBM weekly responder (patient who has a CSBM frequency during the week that is at least 3 CSBMs/week and increase by at least 1 CSBM/week from pretreatment) for 9 out of the 12 weeks.”²¹

The initial determination of a patient being a 12-week CSBM Overall Responder or CSBM Weekly Responder did not incorporate IVRS call compliance. Therefore a patient who had less than 4 IVRS responses in a week could potentially be treated as a responder for the week. If a patient prematurely discontinued from the trial such that the patient’s final Treatment Period week contained less than 4 days, the patient was not considered a CSBM Weekly Responder for that week or the subsequent missed weeks of the Treatment Period. A sensitivity analysis of the primary efficacy endpoint was performed whereby a study participant with less than 4 complete IVRS calls in a Treatment Period week was considered a nonresponder for that week. The primary endpoint (“12 week CSBM Overall Responder”) was then “modified” and a sensitivity analysis based on the new “modified CSBM Weekly Responder” endpoint was performed. The modified weekly and overall CSBM responder endpoints are the endpoints that are currently accepted by the Division as a meaningful clinical outcome for trials conducted in patients with chronic idiopathic constipation.

According to the applicant, the responder rates between each of the Linaclotide dose groups and the placebo group were compared using a Cochran-Mantel-Haenszel test controlling for geographic region. The reader is referred to the statistical review of Dr. Milton Fan for additional information on the statistical analysis plan.

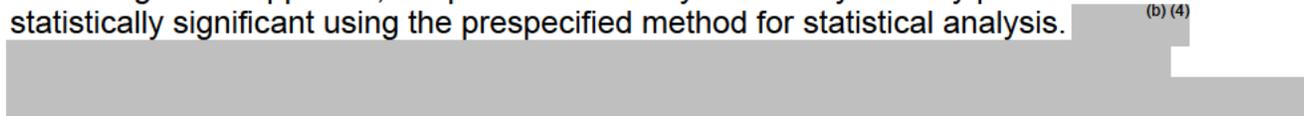
6.1.5 Analysis of Secondary Endpoints(s)

The study endpoints and labeling team had recommended that applicants seeking to develop products for chronic idiopathic constipation also include a patient rating of change question which quantifies the patient's assessment of improvement. For both of the trials submitted in support of this application, the statistical analysis plan included a number of prespecified change from baseline assessment of the following parameters:

- 12-week CSBM frequency rate,
- 12-week SBM frequency
- 12-week Stool consistency
- 12-week Severity of Straining
- 12-week Abdominal Discomfort
- 12-week Bloating
- 12-week Constipation Severity

To support the content validity of the selected parameters the applicant interviewed 28 patients with chronic idiopathic constipation in parallel with the Phase 3 trials to determine symptoms most important and bothersome to them. According to the applicant, "both within and across 2 separate rounds of interviews, patients with chronic idiopathic constipation most frequently reported the symptoms of decreased stool frequency, hard stools, straining, incomplete evacuation, abdominal discomfort, bloating, and abdominal pain." Other symptoms mentioned by these patients were considered to be consequences, impacts (e.g., rectal pain, rectal bleeding, and hemorrhoids), or nonspecific symptoms (e.g., headaches, fatigue, and irritability) and therefore were not chosen as additional efficacy assessment. During the development of the PRO-Dossier for Chronic Constipation, the sponsor also used an anchor-based approach to determine a "clinically meaningful" change in each parameter.

In previous interactions between the Division and the applicant, the Division has agreed that an average increase from baseline of 1 CSBM/week in patients with chronic idiopathic constipation may be considered clinically meaningful when coupled with an improvement of constipation (demonstrated as CSBM > 3/week). This is by definition the primary endpoint. The symptom severity assessments were very subjective and in the opinion of this reviewer difficult to interpret. For example, during the Pretreatment and Treatment Period daily IVRS calls, patients answered a series of questions about the severity of their abdominal symptoms. Using a 5 point ordinal scale, patients rated their "abdominal pain" "abdominal discomfort" and "bloating" as "None" (1), "Mild" (2), "Moderate" (3), "Severe" (4) or "Very Severe" (5) over the preceding 24 hours. In some questions, patients were asked to reflect on the state of their condition prior to initiation of the trial. With each progressive week, the level of recall bias may have increased, further making these results less useful for interpretation. According to the applicant, the p value for all key secondary efficacy parameters was statistically significant using the prespecified method for statistical analysis. (b) (4)



(b) (4). The reader is referred to the review of the biostatistician for more information. The results of the 7 key secondary efficacy parameters are included in the table below..

Table 57 Overview of Results of Prespecified Key Secondary Efficacy Variables Pooled Phase 3 Double-Blind Placebo Controlled Trials (LIN-MD-01 & MCP-103-303) In Chronic idiopathic constipation Patients

Parameter	Mean Baseline	Placebo (N = 423) LS Mean Change (SE)	Linaclotide			
			145 µg (N = 430)		290 µg (N = 418)	
			LS Mean Change (SE)	LSMD (95% CI)	LS Mean Change (SE)	LSMD (95% CI)
CSBMs/Week	0.3	0.5 (0.2)	1.9a (0.2)	1.4 (1.1, 1.8)	2.3a (0.2)	1.8 (1.5, 2.2)
SBMs/Week	2.0	1.0 (0.2)	3.1a (0.2)	2.1 (1.7, 2.6)	3.2a (0.2)	2.2 (1.8, 2.7)
Stool Consistency (BSFS Score)	2.4	0.6 (0.1)	1.8 (0.1)	1.3 (1.1, 1.4)	1.9 (0.1)	1.3 (1.2, 1.5)
Severity of Straining (5-Ordinal point Scale)	3.2	-0.5 (0.0)	-1.1 (0.0)	-0.6 (-0.7, -0.5)	-1.2 (0.0)	-0.6 (-0.7, -0.6)
Abdominal Discomfort (5-point Ordinal Scale)	2.5	-0.3 (0.0)	-0.5 (0.0)	-0.2 (-0.3, -0.1)	-0.5a (0.0)	-0.2 (-0.2, -0.1)
Bloating (5-point Ordinal Scale)	2.8	-0.2 (0.0)	-0.4 (0.0)	-0.2 (-0.3, -0.1)	-0.4 (0.0)	-0.2 (-0.3, -0.1)
Constipation Severity (5-point Ordinal Scale)	3.3	-0.3 (0.0)	-0.9 (0.0)	-0.6 (-0.7, -0.5)	-0.9a (0.0)	-0.6 (-0.7, -0.5)

Source: Table 3.2.2-2 Applicant's Integrated Summary of Efficacy page 65.

The CC Phase 3 Pooled ITT Population consists of all patients in the ITT Populations for the two Phase 3 double-blind, placebo-controlled, CC trials. The mean change from baseline is a least-squares mean change based on an ANCOVA model with trial, treatment group and geographic region as factors and baseline value as covariate.

Baseline is the mean value for the combined ITT Population from both Phase 3 studies.

CI = confidence interval; SE = standard error of LS mean.

LSMD, and 95% CI are based on a pairwise comparison vs. placebo from the ANCOVA model.

6.1.6 Other Endpoints

There were a number of additional efficacy parameters that were measured in both of the Phase 3 trials. The following table reproduced from the applicant's submission outlines the additional efficacy parameters. The reader is referred to the statistical review of Dr. Milton Fan for information related to the statistical significance of these variables.

Table 58 Additional Efficacy Parameters in the Phase 3 Double-Blind Placebo Controlled Chronic idiopathic constipation Trials

<i>Additional Efficacy Parameter</i>	<i>Definition</i>
CSBM Within 24 Hours of First Dose of Study Drug	Patients with a CSBM within 24 hours of first receiving study drug
SBM Within 24 Hours of First Dose of Study Drug	Patients with an SBM within 24 hours of first receiving study drug
CSBM Weekly Responder	Patients who had ≥ 3 CSBMs and a change from baseline of ≥ 1 during the particular week
12-week CSBM Rate ≥ 3 Responder	Patients who had a CSBM rate ≥ 3 for at least 9 out of the 12 weeks
12-week CSBM Rate Change ≥ 1 Responder	Patients who had a CSBM rate that increased by ≥ 1 from baseline for at least 9 out of the 12 weeks
Treatment Period CSBM Rate Change ≥ 1 Responder	Patients who had an overall CSBM rate that increased by ≥ 1 from baseline for the Treatment Period
12-week SBM Responder	Patients who had an improvement from baseline of 2 or more in SBMs/week for at least 9 of the 12 weeks
12-week Stool Consistency Responder	Patients who had a minimum of 2 full categories improvement in Stool Consistency in a week for at least 9 of the 12 weeks.
12-week Severity of Straining Responder	Patients who had a minimum of a full category improvement in Severity of Straining in a week for at least 9 of the 12 weeks.
12-week Constipation Severity Responder	Patients who had a minimum of a full category improvement in Constipation Severity in a week for at least 9 of the 12 weeks
12-week Abdominal Discomfort Responder	Patients who had a minimum of a full category improvement in Abdominal Discomfort in a week for at least 9 of the 12 weeks
12-week Bloating Responder	Patients who had a minimum of a full category improvement in Bloating in a week for at least 9 of the 12 weeks
12-week Constipation Responder	Patient who was a Weekly Constipation Severity Responder for at least 9 out of the 12 weeks of the Treatment Period. A Weekly Constipation Severity Responder was a patient who had an improvement from baseline of 1 or more in Constipation Severity for that week.
12-week Degree of Relief of Constipation Symptoms Responder	Patient whose response was "somewhat," "considerably," or "completely relieved" for all of the 12 weekly assessments for the Treatment Period; or whose response was "considerably" or "completely relieved" for at least 6 out of the 12 weekly assessments
Change From Baseline in 12-week Abdominal Pain	
Use of Per-Protocol Rescue Medicine or Any Other Laxative, Suppository, or Enema	
Treatment Satisfaction	
Treatment Continuation	

Source: Applicant's Table 1.2.11-2 Integrated Summary of Efficacy page 29.

6.1.7 Subpopulations

Sensitivity analyses of the pooled results for the primary efficacy variable were consistent with the primary analysis. Efficacy was established and fairly consistent among subpopulations based on age, race, BMI, and geographic region. Additional information is found in the statistical review. Subanalyses were also conducted while factoring in disease severity, concomitant illnesses, and history of tobacco or alcohol use.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

During the clinical development of Linaclotide, the analytical procedures for determining the Linaclotide content in the clinical trial material were altered resulting in changes to the expression of dose strengths of the clinical trial material. The changes in the analytical procedure were presented to and agreed upon with the FDA. The trial dose strengths of the clinical trial material were initially expressed as 150µg and 300µg, based on the total peptide content. Subsequently using a different analytical method, the dose-strength expressions were updated to reflect the Linaclotide content only, which resulted in the dose strengths of Linaclotide being expressed as 133µg and 266µg, respectively. A third approach to determining the Linaclotide content was utilized later which resulted in an update of the dose-strength expressions from 133 µg and 266 µg to 145µg and 290 µg respectively. According to the applicant these modifications represent changes only in the dose-strength expression, and do not reflect changes in the actual dose-strength administered to patients. According to the clinical pharmacology reviewer and chemistry reviewers, these adjustments were acceptable. Additional analyses of the individual Phase 1 and Phase 2 trials submitted in support of this application are available in the clinical pharmacology review. (Note: Because of the very low systemic availability of the drug, no relative bioavailability or bioequivalent trials were performed.)

The following table, reproduced from the applicant's submission, summarizes the dose-strength expression changes. For the purposes of this review the 145µg and 290µg dose expressions are used.

Table 59 Table Summarizing Dose-Strength Expression Changes in LIN-MD-01

Original Dose (based on total peptide content)		Revised Dose 1 (based on Linaclotide content)		Revised Dose 2 (based on Linaclotide content)	
150 µg	300 µg	133 µg	266 µg	145 µg	290 µg

The Phase 3 doses for the CIC clinical program were chosen based on the results of the Phase 2-dose ranging trials. The two Phase 2b trials evaluated Linaclotide 72µg, 97µg, 145µg, 290µg, 579µg and 966µg doses. The 290µg dose was selected because it demonstrated efficacy similar to the 579µg dose but had a lower incidence of diarrhea. The 145µg dose was chosen because it demonstrated efficacy over placebo and was presumed to have a better safety profile than the 290µg dose.

During the double-blind Phase 3 trials, both the 145µg and 290µg Linaclotide doses were administered once daily prior to the first meal of the day. Interruption of study drug was permitted up to 3 days if a patient experienced an AE. If, after restarting therapy, the person experienced another adverse event that required interruption of treatment, that patient was withdrawn from the trial. The Linaclotide 290µg dose was used as the starting dose in the long-term safety trials. Dose reduction to 145µg was allowed for patients who experienced an adverse event.

In a food-effect study, IBS-C patients treated for seven days with once-daily 290µg Linaclotide administered after a high-fat breakfast had looser stools (as evidenced by increased numbers on Bristol Stool Form Scale) and increased stool frequency compared with fasted patients who were administered the drug. This suggests that food increases the pharmacodynamics of Linaclotide. All doses of Linaclotide in the Phase 3 trials were administered 30 minutes prior to breakfast.

The applicant asserted that the Phase 2 and 3 program suggests that the difference in efficacy between the 145µg and the 290µg doses suggests that there are patients with chronic idiopathic constipation who are more likely to benefit from receiving the 290µg dose. However the results of the individual Phase 3 trials were conflicting. (Please refer to Section 6 of this review.) For the primary efficacy variable (CSBM overall responder), 20.5% of patients in the Linaclotide 290µg group were CSBM overall responders and 15.5% of the Linaclotide 145µg group were CSBM overall responders in trial LIN-MD-01. However, in Trial MCP-103-303, the 19.4% of patients in the Linaclotide 290µg group were overall responders, while 20.3% of patients in the Linaclotide 145µg group were overall responders. The results accounted for IVRS compliance. The trials were not designed to assess the superiority (or inferiority) of the Linaclotide doses when compared to each other.

A subgroup analysis based on baseline disease characteristics, demographic data, and constipation symptoms respectively, while using the primary endpoint as the response variable was conducted to identify which patients would be more likely to benefit from the 290µg dose. There were no subgroups identified, based on demographics (i.e. race, age, gender, ethnicity), that had meaningful differences in response to the Linaclotide 145µg and 290µg doses for the primary responder endpoint.

The treatment difference between the primary endpoint responder rates and placebo for the 145µg and 290µg Linaclotide doses are presented in the table below.

Table 60 Treatment Difference Overall Responder CSBM Rates Pooled Data Phase 3 Double-Blind CIC Trials ITT Population

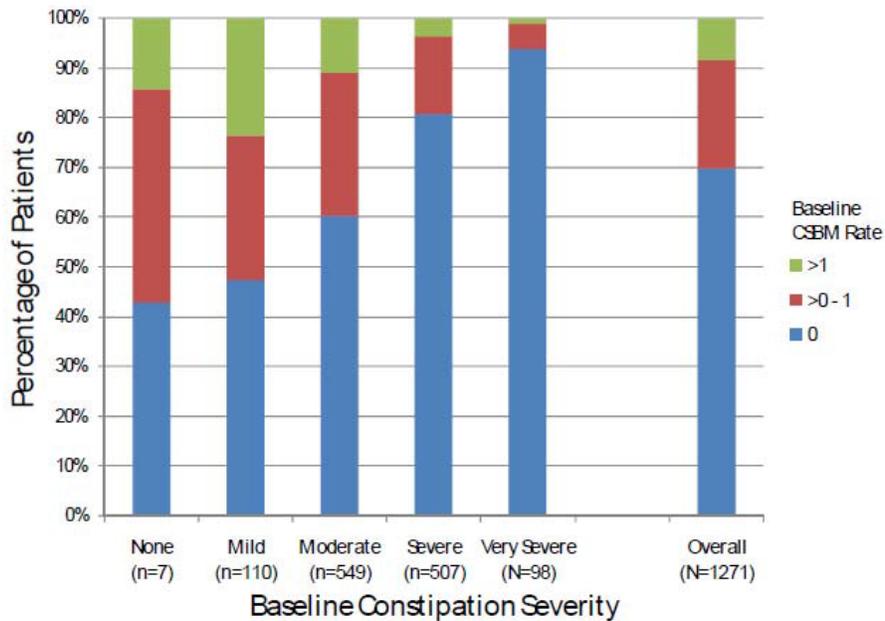
Change from Baseline CSBM Rate	145 ug - Placebo Treatment Difference (95%CI)	290 ug - Placebo Treatment Difference (95%CI)
ITT Population	13.9% (9.68, 18.07)	15.6% (11.25, 19.96)

Source: Table R502.1.1 and Table 2.2 Applicants Submission Response to Information Request May 07, 2012.

Patients with chronic idiopathic constipation rated the severity of their constipation symptoms at baseline and for each week during the trial. "Constipation severity" was assessed as none, mild, moderate, severe and very severe. (To assess the rating of constipation severity, patients were asked, "On average, how would you rate your constipation during the past 7 days. A 5-point ordinal scale was used where patients chose either 1=none; 2=mild; 3=moderate; 4=severe; 5=very severe.) The pooled efficacy data were reanalyzed stratifying by baseline "constipation severity" as indicated by the patients. (b) (6)

Patients were not given pre-specified criteria to aid in defining "severe" and the term is inherently subject. It is difficult to know if one patient's definition of constipation severity is the same as another person's definition of constipation severity. Exploratory analysis was performed to assess patients' perception of severity at baseline. When one looks at the mean constipation of severity, as assessed by the patients at baseline and across the 12 weeks of Treatment for both Trials LIN-MD-01 and MCP-103-303, it is apparent that on average patients enrolled in both trials described their constipation severity as "moderate" at baseline. (Mean baseline constipation severity score was 3.3 (moderate) for both Trials LIN-MD-01 and MCP-103-303. Refer to Figures below.) In the combined pooled population, approximately 43% (549/1271) reported that baseline constipation severity as "moderate" and approximately 40% (507/1271) reported their baseline constipation severity as "severe". Interestingly, 70% (887/1271) of patients in the ITT population had a baseline CSBM frequency rate of 0 CSBMs/week. Approximately 60% of those who described their baseline constipation severity as "moderate" had 0 CSBMs/week at baseline, while 81% who described their baseline severity as "severe" had 0 CSBMs/week at baseline. Therefore it appears that "severe constipation symptoms" does not necessarily equate to 0 CSBMs/week at baseline. When assessing only those patients that had a 0 CSBMs/week at baseline (887 patients), 37% (331/887) described their baseline severity as "moderate", while 46% (409/887) described their constipation severity as "severe".

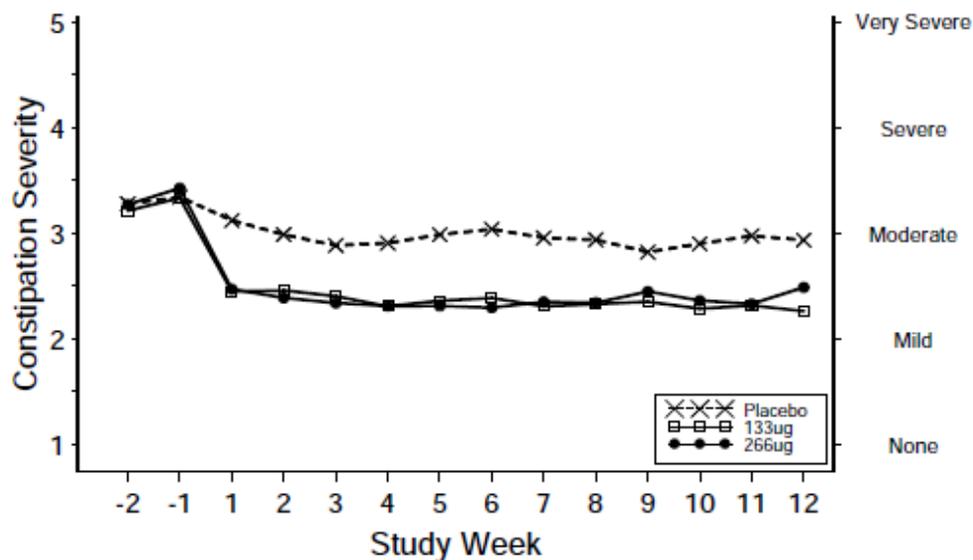
Figure 12 Distribution of Baseline CSBM Frequency by Baseline Constipation Severity



Note: CC Phase 3 Pooled ITT Population

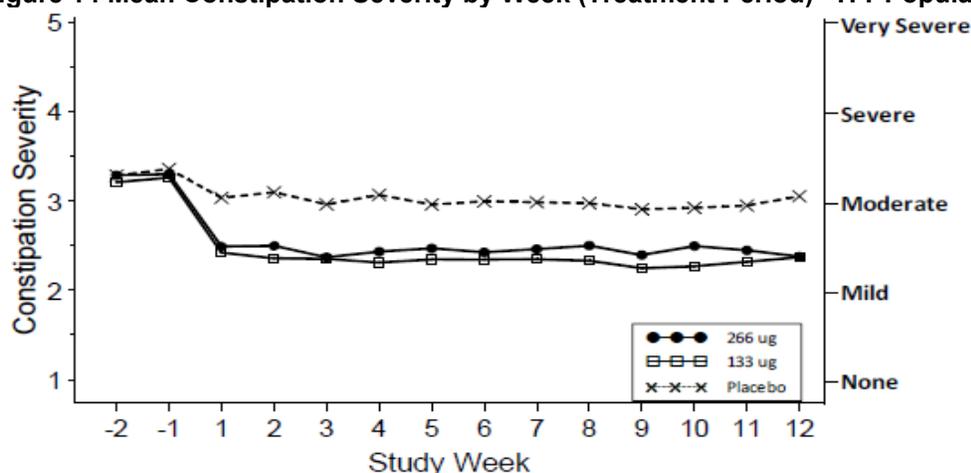
Source: Figure 3.1. Applicants Submission Response to Information Request May 7, 2012.

Figure 13 Mean Constipation Severity by Week (Treatment Period) - ITT Population LIN-MD 01.



Source: Table 11.4.1.3.7-1 and Figure 11.4.1.3.7-1 Applicant's Clinical Study Report of Trial LIN-MD-01 pages 106 and 107.

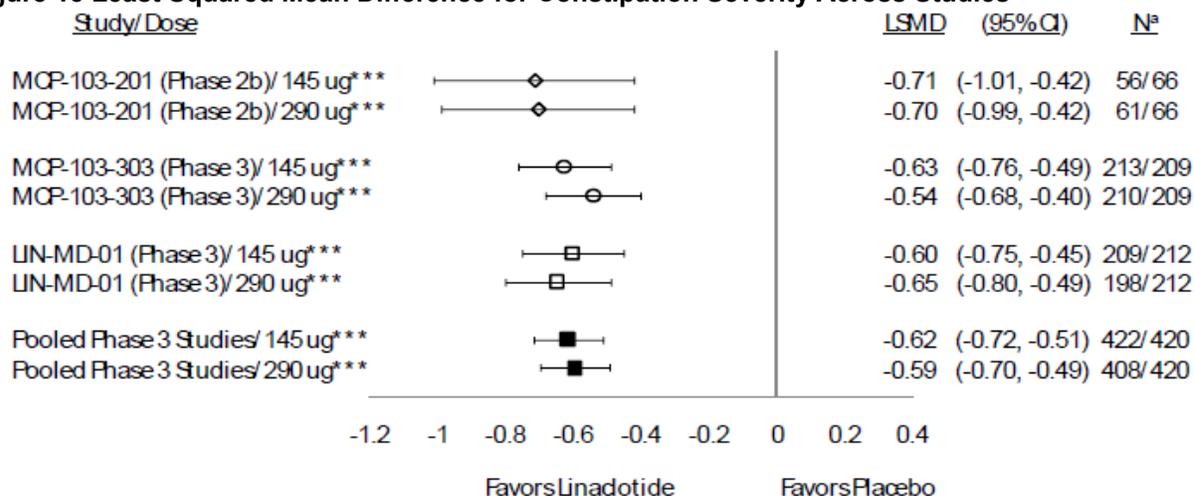
Figure 14 Mean Constipation Severity by Week (Treatment Period) - ITT Population MCP-103-303



Source: Table 20 and Figure 12 Applicant's Clinical Study Report of Trial MCP-103-303 pages 124 – 125.

This reviewer agrees that the least squared mean difference between each dose of Linaclotide and placebo for the “Constipation Severity” efficacy parameter was statistically significant. The results of the Phase 3 pooled data from the ITT population were similar to the results from the individual Phase 2b and Phase 3 trials, showing a clear separation between Linaclotide and placebo. However, significant differentiation between the 145µg and 290µg doses of Linaclotide was not observed for this parameter and is unlikely to be clinically meaningful. (Refer to the following figure.)

Figure 15 Least Squared Mean Difference for Constipation Severity Across Studies



*** p < 0.0001

p-value, LSMD, and 95% CI are based on a pairwise comparison vs placebo from the ANCOVA model.

LSMD = least squares mean difference; CI = confidence interval

a. Linaclotide group/placebo; ITT population is presented.

Note: For Phase 3 and CC Phase 3 Pooled, the Constipation Severity parameter is based on a 12-week Treatment Period; for Phase 2b, the Constipation Severity parameter is based on a 4-week Treatment Period.

Source: Figure 3.2.4.7-1 Applicant's Integrated Summary of Efficacy page 78.

Notwithstanding constipation severity, the applicant makes a somewhat stronger inductive argument for use of the 290µg dose in patients with chronic idiopathic constipation who have 0 CSBMs/week or < 1SBM/week at baseline. The treatment difference in Overall CSBM responder rates stratified by baseline CSBM rates is presented in the table below. There was a greater treatment difference in the Linaclotide 290µg group relative to the 145µg dose group in those patients that had 0 CSBMs at baseline. However, as noted previously the majority of patients in both trials had baseline weekly CSBM rates equal to 0.

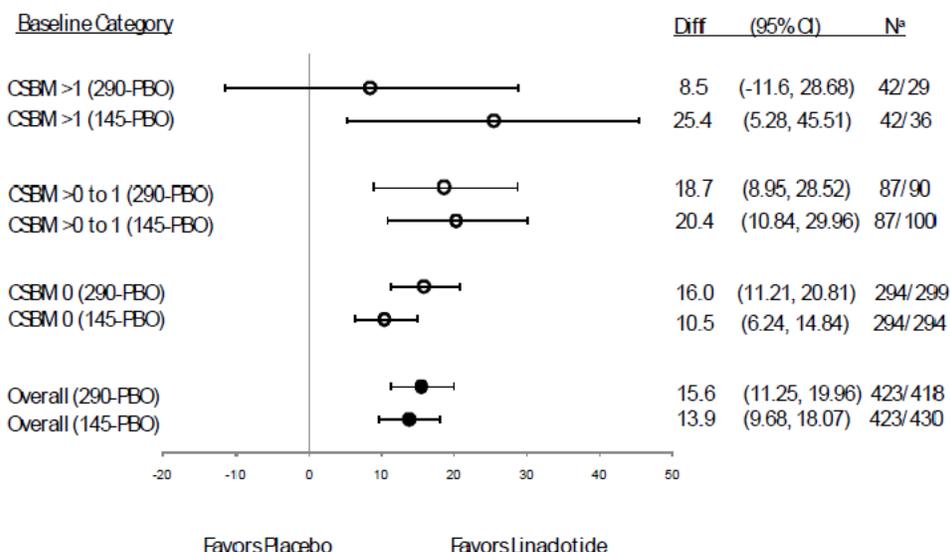
Table 61 Treatment Difference Overall CSBM Responder Rates Stratified by Baseline CSBM Rates Pooled Phase 3 CIC Trials ITT Population

Baseline CSBM Rate	145 µg - Placebo Treatment Difference (95%CI)	290 µg - Placebo Treatment Difference (95%CI)
0	10.5 (6.24, 14.84)	16.0 (11.21, 20.81)
> 0 to 1	20.4 (10.84, 29.96)	18.7 (8.95, 28.52)
> 1	25.4 (5.28, 45.51)	8.5 (-11.60, 28.68)

Source: Table 2.2 Applicants Submission Response to Information Request May 7, 2012.

The following figuratively represents the treatment differences in Overall CSBM Responder rate Stratified by Baseline CSBM.

Figure 16 Treatment Difference Overall CSBM Responder Rate Stratified by Baseline CSBM Rate Pooled Phase 3 CIC Double Blind Trials ITT Population

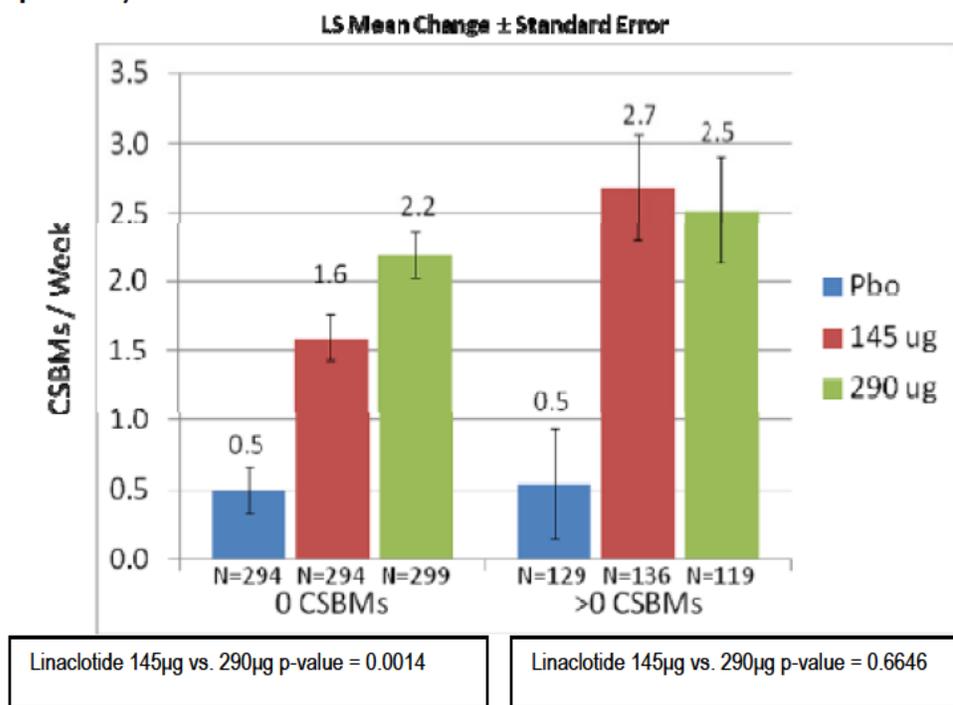


Source: Figure 2.1 Applicants Response to Information Request May 7, 2012.

However, an analysis of the secondary efficacy parameter, “Change from Baseline in 12-week CSBM Frequency Rate” by baseline CSBM frequency rate showed that among patients

who had 0 CSBMs/week at baseline, those who received the 290µg dose had a least-squared mean change of 2.2 CSBMs/week from baseline compared with a least-squared mean change of 1.6 CSBMs/week for those who received the 145µg dose ($p = 0.0014$). Among patients who had <1 SBM/week at baseline, those who received the 290µg dose had a least-squared mean change of 1.8 CSBMs/week from baseline, versus the 1.3 CSBMs/week for those who received the 145µg dose. While the results are statistically significant, it is not entirely clear that having an extra 0.5 - 0.6 CSBM per week will be clinically meaningful to a patient and there is no evidence to support this assertion.

Figure 17 12-Week Change from Baseline in CSBMs stratified by Baseline CSBMs (Pooled CIC Phase 2 ITT Population)

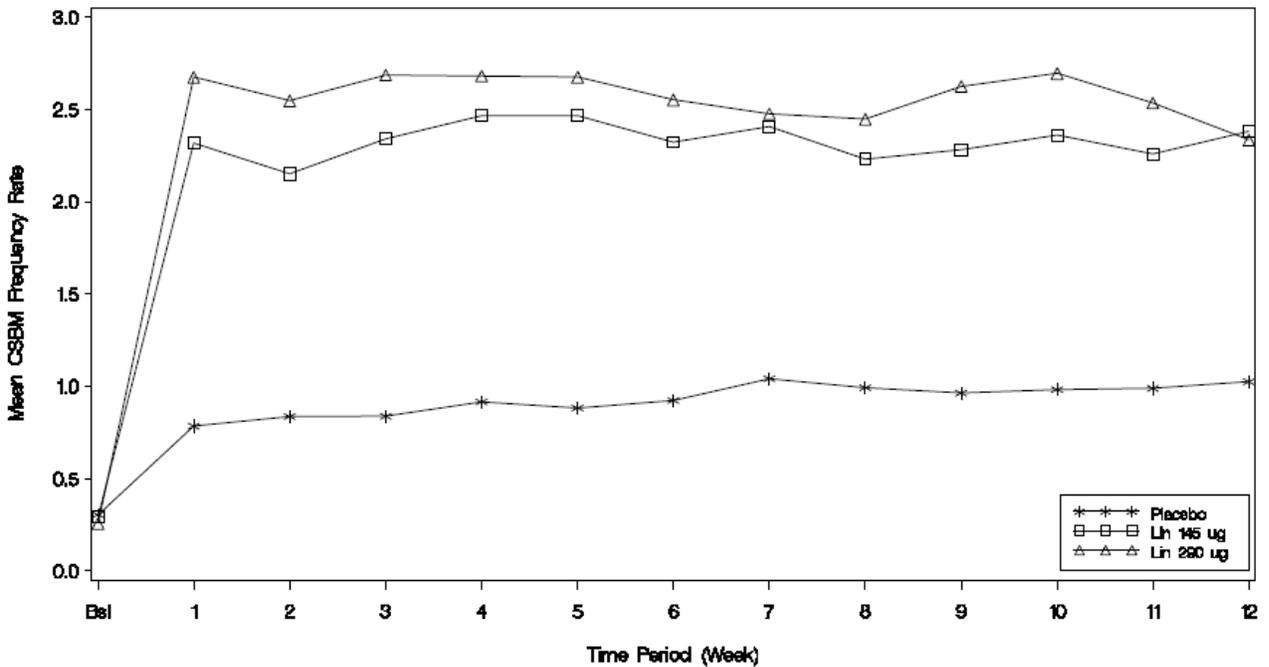


Source: Figure 1-1 page 6 Applicant's Response to Information Request dated April 10, 2012.

Assuming that the 290µg dose of Linaclotide produces greater receptor occupancy and therefore a greater PD response than the 145µg dose as suggested by the Phase 2 dose ranging trials, it is not entirely clear why the change from baseline in CSBMs/week would not consistently correlate with dose (irrespective of baseline CSBMs).

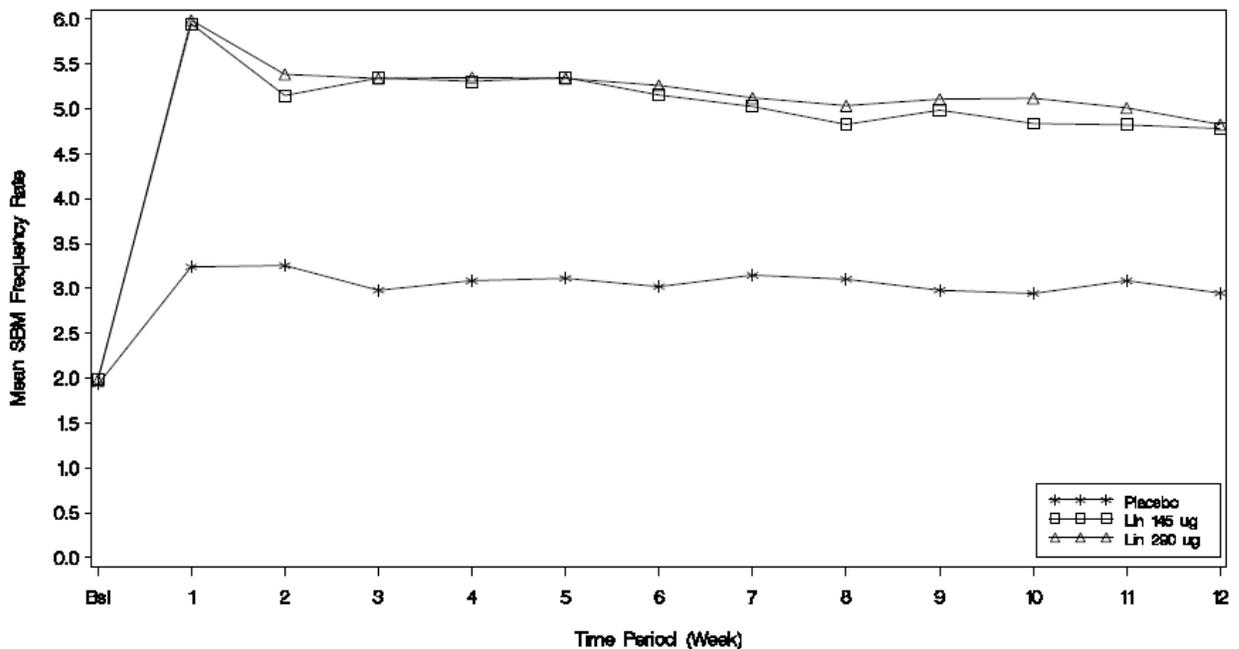
The reviewer also assessed the mean CSBM frequency rates and mean SBM frequency rates of the 145µg and 290µg doses at baseline and across the 12 week Treatment period. While the analysis does indicate that the mean CSBM rate for the 290µg dose is higher than the 145µg dose for all Treatment Period weeks except at Week 12, the difference between the two doses is less than 1 CSBM/week. Again, it is not clear that this will represent a meaningful clinical difference. The mean SBM rates in the 290µg dose group are either slightly higher or equivalent to the 145µg dose group. (See Figures below.)

Figure 18 CSBM Frequency Rate by Week Pooled Phase 3 CIC Data ITT Population.



Source: Figure R502.1.1 Applicant's Response to Information Request dated May 07, 2012.

Figure 19 SBM Frequency Rate by Week Pooled Phase 3 CIC Data ITT Population



Source: Applicant's Submission Figure R502.2.1 Response to Information Request May 07, 2012.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Over the 12 weeks of the Treatment period, efficacy data were analyzed on a weekly basis. For CSBM frequency, SBM frequency, bloating, abdominal discomfort, and constipation severity a separation in the treatment response favoring both Linaclotide doses over placebo was observed in week 1 and maintained over the 12 weeks of the treatment period.

Trial MCP-103-303 also incorporated an additional 4 week Randomized-Withdrawal period to assess for the durability of response to Linaclotide therapy and any possible worsening of baseline symptoms. Patients who had received Linaclotide during the treatment period were re-randomized to receive placebo or continue treatment on the same dose of Linaclotide taken during the treatment period. Patients who had received placebo were re-randomized to receive 290µg of Linaclotide. Linaclotide-treated patients re-randomized to the placebo group had fewer weekly CSBMs and SBMs and returned toward pre-treatment baseline levels within 1 week. There was no evidence of rebound worsening of constipation symptoms. Linaclotide-treated patients who continued on Linaclotide maintained their response to therapy over the additional 4 weeks. Patients on placebo who were re-randomized to Linaclotide 290µg had in an increase in CSBM and SBM frequency similar to the levels observed in patients taking Linaclotide 290µg during the treatment period.

6.1.10 Additional Efficacy Issues/Analyses

The applicant is referred to the statistical review of Dr. Milton Fan for additional post-hoc analyses of primary endpoint using modified responder definitions. Across all post-hoc analyses treatment efficacy was established and results were statistically significant. However, there were minimal differences in the treatment benefit accomplished by the Linaclotide 290µg dose and the Linaclotide 145µg dose over placebo.

7 Review of Safety

Safety Summary

Overall the information presented by the Applicant suggests that Linaclotide is safe and well tolerated for the treatment of patients with chronic idiopathic constipation. A total of 909 patients with chronic idiopathic constipation were treated with Linaclotide for at least 6 months, 745 patients were treated for at least one year. The Phase 3 Double-Blind Placebo Controlled trials enrolled 1275 patients with chronic idiopathic constipation. Demographics were similar across all treatment arms. The majority of patients were Caucasian (76%), female (89%), non-Hispanic (90%) and under the age of 65 years (88%). Almost a third of patients were obese (BMI ≥ 30 kg/m²). Approximately 20% had a history of hypertension, approximately 5% had a history of diabetes, and approximately 3% had a history of cardiovascular disease across all treatment groups. Patients with these comorbid conditions at baseline did not appear to be affected from shifts in fluids and electrolytes that may have been caused by Linaclotide induced diarrhea. Over 90% of patients were taking a concomitant medication and the use of concomitant medications did not impact the adverse event profile. A summary of the adverse events occurring during the double blind trials is presented in the table below.

	Placebo N = 423	LINACLOTIDE 145µg N = 430	LINACLOTIDE 290µg N = 422	LINACLOTIDE TOTAL N = 852
	n (%)	n (%)	n (%)	n (%)
Patients with at Least 1 TEAE	222 (52.5%)	262 (60.9%)	235 (55.7%)	497 (58.3%)
Number of TEAEs	721	872	783	1655
Number of Patients in Each Category of Adverse Event				
Deaths	0	1 (0.23%)	1 (0.23%)	2 (0.23%)
Serious Adverse Event	10 (2.4%)	6 (1.4%)	11 (2.6%)	17 (2.0%)
Adverse events leading to interruption of trial treatment				
≥ 1 Severe TEAEs	24 (5.7%)	26 (6.0%)	31 (7.3%)	57 (6.7%)

The most commonly reported treatment emergent adverse event was diarrhea. Age, ethnicity, and gender did not appear to affect the incidence of adverse events. A slightly higher percentage of Blacks experienced low absolute lymphocyte counts and neutrophil counts. However this did not appear to be treatment related and may be attributed to benign ethnic neutropenia. Analyses of the safety data failed to generate safety signals for ischemic colitis or gallbladder disease. There were no remarkable changes from baseline or potentially clinically significant changes in vital signs, ECGs, or laboratory values.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data from all patients administered Linaclotide during the clinical development program were submitted in this application. To support the safety of Linaclotide for use in both IBS-C and chronic idiopathic constipation (CIC), the applicant submitted data from 13 clinical trials (6 Phase 3 trials, 4 Phase 2 trials, and 3 Phase 1 trials). Background literature was also submitted, however there were no additional secondary sources of evidence provided by the applicant. In all integrated safety summary analyses, the Linaclotide doses used are based on the total Linaclotide content (as opposed to the total peptide content (additional details are provided in Section 4.1)).

For the purpose of the safety evaluation, the safety data was organized into 5 dataset groups based on study phase, study population and study design. The groups were:

- Group 1 (Phase 3 placebo-controlled trials) – 4 Phase 3, double-blind, placebo-controlled trials. Data integrated separately for CIC trials, IBS-C trials, and then for the combined CIC-and IBS-C populations. (Note: Two of the Phase 3 trials included a 4-week Randomized Withdrawal period. Safety data from the RW periods were not included in the Group 1 analysis but were presented in the each of the individual study reports and included in the Group 4 analysis.
- Group 2 (Phase 2 CIC studies) – 2 Phase 2, double-blind placebo controlled CIC trials (Trials MCP-103-004 and Trials MCP-103-201)
- Group 3 (Long-term safety trials) – Interim data from the two ongoing Long-term safety trials. This group included rollover IBS-C and CIC patients from Phase 2 and Phase 3 trials. The group also included patients who were ineligible to take part in prior Phase 3 trials, but fulfilled enrollment criteria for the long-term trials. Data from rollover patients were limited to data obtained following a patient's entry into the long-term safety trials. For the Long-term Safety Trial, the safety information was collected up to and including the cut-off date October 11, 2010.
- Group 4 (All-Linaclotide Patients) -- Only data from Linaclotide-treatment periods (not placebo) were included in this group (i.e. pooled data from all Linaclotide patients in the Phase 2 and Phase 3 trials). Exposure for Group 4 was summarized for the Linaclotide Treatment Periods in the Phase 2 and Phase 3 trials, but excluded Phase 2 lead in exposure of the rollover patients. Safety data for Group 4 were collected from the time of patient's first exposure to Linaclotide, so that data from a lead-in trial for the rollover patients were included in this group. Safety data from patients re-randomized to a Linaclotide dose during the RW period (after taking placebo in the Treatment period) were included in this group.
- Group 4S (Subset of Group 4 that includes Groups 1 and 3 patients only) – Pooled data from all patients receiving Linaclotide except for data from Phase 2 trials.
- Group 5 (Phase 1 trials) – 3 Phase 1 clinical pharmacology trials in healthy patients.

The safety population for Groups 1, 2, and 3 consisted of all patients who had taken at least 1 dose of study drug treatment during the Treatment Period of the trials. The safety population for Groups 4 and 4S consist of all patients who had taken at least 1 dose of Linaclotide during the Treatment Period or Randomized Withdrawal (RW) Period. This review will focus on the safety data from Group 1 (and when appropriate Group 4) for patients with chronic constipation. (Analyses of the Long-term data were presented in the review of Dr. Lara Dimick-Santos.) Analyses of the Randomized-Withdrawal period for trial MCP-103-303 are not presented in the integrated analysis. The reader is referred to section 5.3.3.2 for analysis of the safety data from the randomized-withdrawal period of trial MCP-103-303. Please refer to Section 5, Table 2 for a complete listing of the trials involving patients with chronic idiopathic constipation (CIC).

An enumeration of all patients from all clinical trials contributing data to the safety analysis is provided by Group in the Table below. When data for the Chronic idiopathic constipation Population and IBS-C Population were pooled separately in the applicant's submission, only the data from the Chronic idiopathic constipation group are presented.

Table 62 Enumeration of Linaclotide Patient Exposures for Chronic idiopathic constipation (CIC) Patients in the Linaclotide Clinical Development Program. Data lock: October 11, 2010

Study ID number	Number of Patients					
	Placebo	Linaclotide, ug/d				
		< 145	145	290	> 290	Any dose
Phase 3 Placebo-Controlled Trials (Group 1)						
<i>CIC Patients</i>						
LIN-MD-01 (up to 12 weeks)	215	—	213	205	—	418
MCP-103-303 (up to 12 weeks)	208	—	217	217	—	434
<i>CIC Total (Treatment Period)</i>	423		430	422		852
Placebo-Controlled Phase 2 Studies (Group 2)						
<i>CIC Patients</i>						
MCP-103-004 (up to 2 weeks)	10	12	—	10	10	32
MCP-103-201 (up to 4 weeks)	69	59	56	62	63	240
<i>CIC Total</i>	79	71	56	72	73	272
Open-Label Phase 3 Studies (Group 3)						
<i>CIC Patients</i>						
LIN-MD-02	—	—	523	—	—	523
MCP-103-305	—	—	606	—	—	606
<i>CIC Subtotal</i>	—	—	1129	—	—	1129
All Linaclotide Patients (Group 4)^a						
<i>CIC Patients</i>		71	1519^b	73		1627

Source: Table 5.3-1 Applicant's Integrated Summary of Safety pages 52 – 53.

Note: Table includes duplicate patients.

In Group 3, patients were required to start treatment at 290µg but were allowed to titrate down to 145µg for an intolerable adverse event.

^a Patients could be counted in more than one dose in Group 4.

^b Includes 1424 patients from Phase 3 trials and 95 patients from Phase 2 trials

The sponsors pooling of the data seems appropriate and reasonable. The following table summarizes the analysis groups and analyses performed for each of the groups.

Table 63 Overview of Analysis Groups for Integrated Safety and Efficacy Analysis

Data Analyses	Group 1 (Phase 3 trials)		Group 2 (Phase 2 CC)	Group 3 (Long-term Safety Trials)			Groups 4 and 4S (All Linaclotide Patients)	
	CC & IBS-C Pooled Separately	Pooled (CC + IBS-C)	Pooled (CC)	CC & IBS-C Pooled Separately	Pooled (CC + IBS-C)	Individual Studies Separately	CC & IBS-C Pooled Separately	Pooled (CC + IBS-C)
Patient disposition						X		
Investigational product exposure	X	X	X	X	X	X	X	
Demographics	X	X	X	X	X	X	X	
Concomitant medications	X			X				
AE (basic preferred-term table)	X	X	X	X	X		X	X
AE (severity and relationship to investigational product)	X			X				
Death/SAE/ADO	X	X	X	X	X		X	X
Clinical laboratory	X			X				
Vital signs	X			X				
Electrocardiograms	X			X				
Diarrhea specific	X							
Drug-drug interactions ^a	X							
Drug-disease interaction ^a	X							
Drug-demographic interactions ^a (subgroup analyses)	X							
Dose reduction/suspension analyses				X				

^a Drug-drug interaction, drug-disease interaction, and drug-demographic interaction analyses were performed for adverse events and potentially clinically significant laboratory, vital signs, and ECG data.

ADO = adverse event leading to dropout; AE = adverse event; CC = chronic constipation; IBS-C = irritable bowel syndrome with constipation; SAE = serious adverse event

Source: Table 4.3.1-1 Applicant's Submission Integrated Summary of Safety p.28

During the conduct of the Phase 2 and 3 clinical trials, there were 25 patients who enrolled more than once, either in the same trial or in multiple Phase 2 and 3 trials in violation of entry criteria. A summary of the safety data on these “duplicate” patients was presented separately. All data from duplicate patients were collected during each of the Phase 3 randomized placebo-controlled trials in Group 1 in the same way as data were collected for all other patients. All analyses are based on data available up to the cutoff date of October 11, 2010. The analyses of data presented included all data from duplicate patients. Because duplicate patients may have been counted in more than 1 trial, when the data were pool, the number of patients in the pooled totals may not add up to the to the number of patients from the individual trials.

The applicant established rules for inclusion of data from duplicate patients in the “pooled-by-indication” and “overall-pooled analysis” of safety across Phase 3 trials Those rules are provided in the table below.

Table 64 Rules for Inclusion of Data from Duplicate Patients in the ISS Pooled Summaries.

ISS Group	Data Inclusion in the Pooled-by-Indication Summary	Data Inclusion in the Overall (CC + IBS-C)-Pooled Summary
Group 1	Patient data from the first Phase 3 trial in each indication	Patient data from the first Phase 3 trial, regardless of indication (CC or IBS-C)
Group 2 ^a	Patient data from the Phase 2 CC studies for the CC indication summary; not applicable for the IBS-C indication summary	Not applicable
Group 3	Patient data from the first LTS study in each indication into which a duplicate patient rolled over from a preceding Phase 3 trial (or a Phase 2 study if the patient was not in a preceding Phase 3 trial); if the patient was not a roll-over patient, data from the first LTS study in each indication that the patient entered after being randomization ineligible in a Phase 3 trial	Patient data from the first LTS study, regardless of indication, into which a duplicate patient rolled over from a preceding Phase 3 trial (or a Phase 2 study if the patient was not in a preceding Phase 3 trial); if the patient was not a roll-over patient, data from the first LTS study, regardless of indication, that the patient entered after being randomization-ineligible in a Phase 3 trial
Group 4	Patient data for each indication from the Phase 3 trial (if any) and the LTS study (if any) that were included in the ISS Group 1 and Group 3 pooled-by-indication summary, along with data from the Phase 2 study for that indication (if any); only data in the Linaclotide-treatment periods in the studies were included	Patient data from the Phase 3 trial (if any) and the LTS study (if any) that were included in the ISS Group 1 and Group 3 overall-pooled summary along with data from the Phase 2 study (if any); only data in the Linaclotide-treatment periods in the studies were included

Source: Table 4.3.4.2-1 Applicants Integrated Summary of Safety page.31

ISS = Integrated Summary of Safety; LTS = long-term safety.

7.1.2 Categorization of Adverse Events

According to the applicant, all adverse events (AEs) were coded using Version 13.0 of the Medical Dictionary for Regulatory Activities (MedDRA) across all trials in Groups 1, 2, and 3. For any trial in which the AEs were coded using an older version of MedDRA, the AEs were re-coded using Version 13.0. Adverse events were classified by system organ class (SOC) and preferred term. The appropriateness of the applicant's coding was assessed by examining the ADAE datasets submitted with the application. and comparing the preferred terms in the "AEDECOD" column to the verbatim terms reported by investigators and recorded in the "AETERM" column. In general the coding appeared to be adequate for review. There was some splitting of preferred terms. When appropriate, the medical officer combined preferred terms (e.g. abdominal pain vs. abdominal pain upper or abdominal pain lower; diarrhea vs. frequent bowel movements; anemia vs. hematocrit decreased vs. red blood cell count decreased).

For the double blind Placebo-Controlled Trials, an AE in the Treatment Period was considered a treatment emergent adverse event (TEAE) if the onset date was on or after the date of the first dose of the double-blind investigational product in the Treatment Period and it was not present prior to the date of the first dose of the study product in the Treatment Period. An event present prior to the date of the first dose of double-blind study product treatment was considered a TEAE if it worsened in severity following the first dose of study drug.

An AE in the Randomized Withdrawal (RW) period was considered a TEAE if its onset was on or after the date of the first dose of double-blind investigation product in the RW period and it was not present before the date of the first dose of the Treatment Period. An event which began prior to the first dose of double-blind investigational product for the Treatment period was considered a TEAE in the RW period if it increased in severity on or after the date of the first dose of the double-blind product in the RW period.

If more than 1 AE with the same preferred term was reported, the AE with the greatest severity was used as the baseline for comparison. According to the submission, "If more than 1 event occurred during the study with the same preferred term for the same patient, the patient was counted only once for that preferred term using the most severe occurrence for the summarization by severity and using the most related occurrence for the summarization of relationship to the investigational product." Throughout the clinical development program, only AEs that occurred within 1 day of the last dose of double-blind product were counted as a TEAE. An AE that occurred more than 1 day after the last dose was not counted as a TEAE for that period. Exceptions to this general rule were AEs that occurred within 1 day after the last dose of study product in the Treatment Period and concurrently after the first dose of double-blind investigational product in the RW Period or the first dose of open-label study product in the long-term safety trial. These AEs were not considered TEAEs for the Treatment Period even though they started within a day of the last dose of double-blind investigational product in the Treatment Period. Because the first dose of the product in the RW period or the Treatment Period of the Long-Term Safety trial was more proximal to the

AE, the AE was counted as TEAEs either in the RW Period or the Treatment Period of the Long-Term Safety trial.

Common events were defined as TEAEs that occurred in $\geq 2\%$ of patients in any Linaclotide group and were summarized by SOC and preferred term in Groups 1 and 2. In Groups 3 and 4S, TEAEs occurring in $\geq 5\%$ of Linaclotide patients were summarized by SOC and preferred term. Those Linaclotide TEAEs that occurred at an incidence less than or equal to the incidence seen in placebo were not included in safety summary tables.

For Group 1, the TEAEs were summarized by SOC and preferred term and by AE onset time as follows: 0 to 4 weeks, 4 to 12 weeks, >12 weeks from the date of the first dose of double-blind investigational test product.

Dose adjustments were permitted for patients in the long-term safety trials. (Please refer to the review of Dr. Dimick-Santos for additional information.) The number and percentage of patients with Adverse Events leading to dose adjustments were summarized by SOC and preferred term. In addition, the number and percentage of patients who prematurely discontinued from the long-term safety trials were summarized for different dose adjustment patterns by the following discontinuation reasons: GI SOC AE, Non-GI SOC AE, and Other reasons. The "GI SOC AE" was subdivided further into "Diarrhea AE" and "Non-diarrhea GI SOC AE".

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

Please refer to section to section 7.1.1 above. For the purpose of the safety evaluation, the safety data appeared to be appropriately organized into groups based on study phase, study population and study design.

7.2 Adequacy of Safety Assessments

The safety assessments performed by the applicant were adequate to assess a drug of this pharmacological class for adult use. The safety database included demographic and other baseline characteristics; exposure to study drug; adverse events (AEs), clinical laboratory measures; vital signs; electrocardiographic (ECG) assessments; medical/surgical history, and prior concomitant medications. The applicant also included analysis tables of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events leading to withdrawal, and deaths. Drug-related analyses of AEs were presented as "Related" or "Not Related". Relationship was further categorized as "Possible", "Probable" or "Definite" (if considered Related) and "Unrelated" or "Unlikely" (if considered Not Related). Planned safety analyses were presented previously in tabular form under the Methods Section 7.1.

Because the mechanism of action of Linaclotide involves the excretion of chloride and bicarbonate into the intestinal lumen and may result in prolonged diarrhea leading to metabolic acidosis and dehydration, performing an analysis of electrolyte shifts was essential for this investigational product. A thorough TQT studies does not appear to be necessary for

Linaclotide given its limited systemic absorption. However, performing ECGs does appear to be reasonable and sufficient for evaluation of potential cardiac rhythm disturbances that may be associated with Linaclotide use. In addition, the applicant also performed a special analysis of adverse events of special interest including diarrhea, ischemic colitis, and biliary disease. It appears that the applicant has performed all tests that were reasonably applicable to assess the safety of the use of this new drug in adults.

(b) (6)

According to the nonclinical reviewer, at this time there are juvenile animal data from mice that correspond to pediatric ages 0 to 23 months and 12 to 16 years. There are a lack of nonclinical data to support testing Linaclotide in pediatric patients ages 2 – 12 years. Additional nonclinical data and safety assessments covering the full spectrum of the pediatric age range should be required prior to initiating pediatric clinical trials.

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

For additional details of the baseline demographics for the individual Phase 3 chronic idiopathic constipation clinical trials submitted with this application, the reader is referred to Sections 5.3.2 and 5.3.3.

To evaluate the adequacy of clinical experience with a new drug, the reviewer referred to the ICH-E1A guidance “The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions.” This guideline recommends that 300 to 600 participants be treated for 6 months at dosage levels intended for clinical use; 100 participants be exposed for at least 1 year, and a total of 1500 participants be exposed to the new drug.

Exposures to Linaclotide were summarized for patients relative to treatment duration in terms of days of treatment and total exposure (expressed as patient-years). Patient-years were calculated as the sum of the treatment durations of all patients in a group (or study) divided by 365.25. Treatment duration is also presented based on dose-reduction patterns (e.g. decrease dosing from 290µg to 145µg).

When one examines chronic idiopathic constipation patient exposure to Linaclotide across all studies in the development program, the applicant appears to have exceeded ICH-E1A guidelines. The table below summarizes exposures across all Linaclotide treated patients with chronic idiopathic constipation in the 10 Phase 2 and 3 clinical trials of the development program. 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. (The reader is referred to Section 7.1.1 for a table of the number of patients exposed to Linaclotide in the Linaclotide clinical program.) Of the 4370 patients in the Linaclotide clinical program (as of the October 11, 2010 data lock), 1627 were patients with chronic idiopathic constipation. There were 909 patients with chronic idiopathic constipation treated for at least 6 months and 745 patients with chronic

idiopathic constipation treated for at least 1 year. In the Phase 3 open label long-term safety trials, there were 1129 patients with chronic idiopathic constipation exposed to Linaclotide. Total exposure time of the 1627 patients with chronic idiopathic constipation to Linaclotide was 1331 patient-years.

Table 65 Patient Exposure to Linaclotide Across all Studies (Group 4) Integrated Summary of Safety - Safety Populations

	All Double Blind CC patients (includes Phase 2 and 3) (N = 1299)	CC Long-term Safety Trials (N = 1129)	Total CC Patients (N = 1627)
Treatment duration, days			
Mean	63.3	359.4	298.8
SD	34.1	190.6	236.2
Median	83.0	453.0	270.0
Min. Max	1. 119	1. 570	1. 667
n	1299	1129	1627
Treatment duration, n (%)^a			
≥ 1 day	1299 (100)	1129 (100)	1627 (100)
≥ 7 days	1273 (98)	1115 (98.8)	1595 (98.0)
≥ 30 days	854 (65.7)	1063 (94.2)	1340 (82.4)
≥ 60 days	736 (56.7)	975 (86.4)	1207 (74.2)
≥ 120 days	0	891 (78.9)	975 (59.9)
≥ 180 days	0	853 (75.6)	909 (55.9)
≥ 240 days	0	798 (70.7)	840 (51.6)
≥ 360 days	0	715 (63.3)	745 (45.8)
≥ 540 days	0	220 (19.5)	459 (28.2)
≥ 720 days	0	0	0
Patient-years	225.2	1110.9	1331

Source: Applicants Table 5.3.4-1 Integrated Summary of Safety page 57 and After-text Table 16.1, page 3039.

Group 4 (All Linaclotide-Treated Patients) is based on Group 1 (i.e., LIN-MD-01, MCP-103-303, LIN-MD-31, and MCP-103-302),

Group 2 (i.e., MCP-103-201 and MCP-103-004), Group 3 (i.e., LIN-MD-02 and MCP-103-305), and studies MCP-103-202 and MCP-103-005.

The summary is based on the Linaclotide-treatment periods, including Linaclotide-treatment-RW period, of Group 4 patients.

Treatment duration in the treatment period = date of last dose of Linaclotide in the treatment period - date of first dose of Linaclotide in the treatment period + 1.

Treatment duration in the RW period = date of last dose of Linaclotide in the RW Period - date of first dose of Linaclotide in the RW period + 1.

Treatment duration for Double-Blind = Treatment duration in the treatment period + Treatment duration in the RW period.

Treatment duration for LTSS = date of last dose of open-label study drug - date of first dose of open-label study drug - number of days that the patient had a temporary dosing suspension + 1.

Patient-years exposure = total amount of time exposed to study drug, expressed in years.

Total = Double-Blind + LTSS, in which a patient who enrolled in more than 1 Group 4 study was counted once.

N = number of patients in the Safety Population.

SD = standard deviation; Min = minimum; Max = maximum.

In Phase 3 placebo-controlled double blind trials for chronic idiopathic constipation (Group 1), there were 852 patients exposed to one of the to-be-marketed doses (145µg or 290µg) of Linaclotide during the treatment period. The mean exposure in the double-blind constipation

trials was comparable for the placebo-treated patients (79 days) and Linaclotide-treated patients (77 days). According to the applicant over 90% of patients were exposed to trial test product for at least 30 days. Total exposure to placebo was 92 patient-years and total exposure to Linaclotide was approximately 180 patient-years (145µg and 290µg doses combined).

The following table summarizes patient exposure to Linaclotide during Phase 3 double-blind placebo controlled constipation trials by duration of exposure and dose.

Table 66 Patient Exposure to Linaclotide in Double-Blind Phase 3 Placebo Controlled Chronic idiopathic constipation Trials.

Exposure	CC Patients		
	Placebo (N = 423)	Linaclotide	
		145 ug (N = 430)	290 ug (N = 422)
Treatment Duration, Days			
Mean	79.0	77.5	76.7
SD	18.2	20.2	21.1
Median	85.0	85.0	85.0
Min, Max	5, 104	1, 102	1, 111
Treatment Duration, n (%)			
≥ 1 day	423 (100)	430 (100)	422 (100)
≥ 7 days	421 (99.5)	424 (98.6)	412 (97.6)
≥ 14 days	418 (98.8)	415 (96.5)	405 (96.0)
≥ 30 days	398 (94.1)	400 (93.0)	392 (92.9)
≥ 60 days	376 (88.9)	372 (86.5)	364 (86.3)
≥ 90 days	25 (5.9)	20 (4.7)	14 (3.3)
≥ 120 days	0	0	0
≥ 150 days	0	0	0
≥ 180 days	0	0	0
Patient-years	91.5	91.2	88.7

Source: Table 5.3.1-1 Applicant Integrated Summary of Safety page 54; After-text Table 1.1.1. page 3005
 Numbers of patients may not add up due to counting of duplicate patients.
 CC Trials: LIN-MD-01 (Treatment Period = 84 days) and MCP-103-303 (Treatment Period = 84 days)

Demographics and other baseline characteristics of patients with chronic idiopathic constipation in the Phase 3 placebo-controlled trials are tabulated below. Baseline characteristics were similar between placebo and Linaclotide treatment groups. The mean age was approximately 48 years across all treatment groups. Only 13% of patients in the double-blind trials were over the age of 65 years. Because the prevalence of chronic idiopathic constipation increases with age, the small percentage of elderly patients in the

trials may limit the generalizability of the results to the broader patient population that is most likely to use the drug outside of the clinical trial setting.

The majority of patients were Caucasian (76%), female (89%), and non-Hispanic (90%). Almost a third of all the patients with chronic idiopathic constipation were obese (BMI \geq 30 kg/m²). There was a slightly higher percentage of patients in the placebo group who were obese relative to the Linaclotide groups. Approximately 20% of trial enrollees had a history of hypertension, approximately 5% had a history of diabetes, and approximately 3% had a history of cardiovascular disease across all treatment groups. The small percentage of patients with diabetes and hypertension is somewhat surprising when one considers that a third of patients were obese.

Table 67 Demographics and Baseline Characteristics of the Phase 3 Chronic idiopathic constipation Double-Blind Placebo-Controlled Trials (Group 1) Safety Population.

Characteristic	CC Patients		
	Placebo (N=423)	Linaclotide	
		145 ug (N = 430)	290 ug (N = 422)
Age (years)			
mean ± SD	48.2 ± 13.9	47.8 ± 13.3	47.5 ± 13.8
≥ 65, n (%)	55 (13.0)	51 (11.9)	49 (11.6)
Sex, n (%)			
Male	46 (10.9)	44 (10.2)	52 (12.3)
Female	377 (89.1)	386 (89.8)	370 (87.7)
Race, n (%)			
Caucasian	327 (77.3)	332 (77.2)	313 (74.2)
Black	88 (20.8)	87 (20.2)	98 (23.2)
Other	8 (1.9)	11 (2.6)	11 (2.6)
Ethnicity, n (%)			
Hispanic	36 (8.5)	42 (9.8)	49 (11.6)
Non-Hispanic	387 (91.5)	388 (90.2)	373 (88.4)
Weight (kg), mean ± SD	77.2 ± 18.2	75.8 ± 17.2	75.8 ± 16.4
Height (cm), mean ± SD	165.0 ± 8.3	164.8 ± 8.1	165.3 ± 8.5
BMI group, n (%)			
< 30 kg/m ²	279 (66.0)	305 (70.9)	306 (72.5)
≥ 30 kg/m ²	144 (34.0)	125 (29.1)	116 (27.5)
Hypertension, n (%)			
Yes	92 (21.7)	90 (20.9)	78 (18.5)
No	331 (78.3)	340 (79.1)	344 (81.5)
Diabetes mellitus, n (%)			
Yes	22 (5.2)	22 (5.1)	23 (5.5)
No	401 (94.8)	408 (94.9)	399 (94.5)
Cardiovascular disorders[±], n (%)			
Yes	15 (3.5)	9 (2.1)	13 (3.1)
No	408 (96.5)	421 (97.9)	409 (96.9)

[±] Cardiovascular Disorders includes the high-level group terms coronary artery disease, myocardial disorders, and heart failures. Numbers may not add up due to counting of duplicate patients. CC Trials: LIN-MD-01 and MCP-103-303. BMI = Body Mass Index
 Source: Table 6.1-1 Applicants Submission Integrated Summary of Safety, page 60.

The baseline demographics for all patients with chronic idiopathic constipation treated with Linaclotide are presented in the table below, reproduced from the Applicant's Integrated Summary of Safety after-text Table 2.5.1 page 3118. Consistent with the Phase 3 double-blind trials, patients in the long-term safety trials had a mean age of approximately 48 years. Most were female (87.2%), Caucasian (76.4%), and Non-Hispanic (90.6%). (See clinical review by Dr. Lara Dimick-Santos.)

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Table 68 Demographics and Baseline Characteristics All Linaclotide-Treated Chronic idiopathic constipation Patients (Group 4) Safety Population

Demographic Parameters	CC		
	Double Blind (N=1299)	LTSS (N=1129)	Total (N=1627)
Age (years)			
Mean	47.8	48.2	47.9
SD	13.5	13.3	13.6
Median	48.0	48.0	48.0
Min, Max	18, 85	19, 87	18, 87
n	1299	1129	1627
Age group, n (%)			
<65 years	1152 (88.7)	998 (88.4)	1434 (88.1)
>= 65 years	147 (11.3)	131 (11.6)	193 (11.9)
>=65 and <75 years	119 (9.2)	102 (9.0)	153 (9.4)
>=75 years	28 (2.2)	29 (2.6)	40 (2.5)
Sex, n (%)			
Male	138 (10.6)	144 (12.8)	184 (11.3)
Female	1161 (89.4)	985 (87.2)	1443 (88.7)
Race, n (%)			
Caucasian	1008 (77.6)	863 (76.4)	1249 (76.8)
African American	253 (19.5)	235 (20.8)	329 (20.2)
Other	37 (2.8)	31 (2.7)	48 (3.0)
Ethnicity, n (%)			
Hispanic	111 (8.5)	106 (9.4)	146 (9.0)
Non-Hispanic	1188 (91.5)	1023 (90.6)	1481 (91.0)
Weight (kg)			
Mean	75.46	76.55	76.12
SD	16.58	17.63	17.23
Median	73.20	73.94	73.48
Min, Max	43.6, 179.5	44.0, 158.8	43.6, 179.5
n	1299	1129	1627
Height (cm)			
Mean	165.13	165.30	165.09
SD	8.12	8.46	8.13
Median	165.00	165.10	165.00
Min, Max	133.4, 203.2	133.4, 203.2	133.4, 203.2
n	1298	1128	1625
BMI (kg/m²)			
Mean	27.65	27.98	27.91
SD	5.58	5.93	5.86
Median	26.90	26.99	27.05
Min, Max	15.1, 69.9	15.1, 55.1	15.1, 69.9
n	1298	1128	1625
BMI group, n (%)			
< 30 kg/m ²	933 (71.8)	779 (69.0)	1133 (69.6)
>= 30 kg/m ²	365 (28.1)	349 (30.9)	492 (30.2)

Group 4 (All Linaclotide-Treated Patients) is based on Group 1 (i.e. LIN-MD-01 and MCP-103-303,); Group 2 (i.e. MCP-103-201 and MCP-103-004), Group 3 (i.e. LIN-MD-02 and MCP-103-305), and trials MCP-103-202 and MCP-103-005.

Total = Double-Blind + LTSS, in which a patient who enrolled in more than 1 Group 4 study was counted once.

BMI = Body mass index, defined as weight in kg divided by height in meters squared.

N = number of patients in the Safety Population. SD = standard deviation; Min = minimum; Max = maximum.

Approximately 90% of patients in the safety population used concomitant medications. The most commonly used concomitant medications across placebo and Linaclotide treatment groups were multivitamins, propionic acid derivatives, anilides, proton-pump inhibitors, HMG CoA reductase inhibitors, progesterones and estrogens, and platelet aggregation inhibitors. There were minor discrepancies in the percentages of concomitant medications across the treatment groups. However, all differences were less than 5% and given the limited systemic availability of Linaclotide, this is not overly concerning and unlikely to significantly impact the safety evaluation.

7.2.2 Explorations for Dose Response

A plasma concentration-response relationship cannot be determined for Linaclotide because of its limited systemic absorption. Therefore, in the absence of clinical pharmacology guidance or biomarkers, dose selection and recommendations were based entirely on two pharmacodynamic (PD) responses observed during the Phase 2 b dose-ranging clinical trials. Both Phase 2b trials evaluated daily Linaclotide doses of 72, 145, 290, and 579 µg versus placebo. According to the applicant, the pharmacodynamic response of orally administered Linaclotide was evaluated in healthy subjects and patients with chronic idiopathic constipation, through bowel symptom assessments of stool consistency (using the Bristol Stool Form Scale [BSFS]), severity of straining (using the seven-point Ease of Passage Scale or a five-point severity of straining scale), stool frequency, and stool weight. Using the BSFS score, patients classified the form or consistency of their stool into one of seven categories, ranging from hard (Type 1) to entirely liquid (Type 7), with Types 3-4 representing the normal form. (Refer to the Appendix). The applicant asserts that because the form of the feces largely depends on the time spent in the colon (i.e., slower transit results in harder stool form), measuring stool consistency using the BSFS is a surrogate for GI transit. Single (29 µg to 2897 µg) and repeated doses (29 µg to 966 µg) of Linaclotide softened stools and decreased straining in healthy subjects relative to placebo. Doses greater than or equal to Linaclotide 290 µg resulted in an exaggerated PD effect. The 290 µg dose was selected because it demonstrated efficacy similar to the 579 µg dose and had a lower incidence of diarrhea. The 145-ug dose was selected because it demonstrated efficacy over placebo and was presumed to have a better safety profile than the 290-ug dose

The results of a food effect trial in IBS-C patients who were administered Linaclotide after a high-fat breakfast demonstrated that food may increase the PD effect of Linaclotide. The PD effect of Linaclotide were also assessed in IBS-C patients using radiographic techniques to measure intestinal transit. The results were that Linaclotide increased colonic transit. Please refer to the clinical pharmacology review.

(b) (6)

the results of the individual Phase 3 trials were conflicting. For the primary efficacy variable (CSBM overall responder), 20.5% of patients in the 290µg Linaclotide group were CSBM overall responders and 15.5% of the 145µg Linaclotide group were CSBM overall responders in trial LIN-MD-01. However, in Trial MCP-103-303, 19.4% of

patients in the 290µg Linaclotide group were overall responders, while 20.3% of patients in the Linaclotide145µg group were overall responders. The trials were not designed to assess the superiority (or noninferiority) of the Linaclotide doses when compared to each other. A subgroup analysis was conducted to identify a subset set of patients more likely to benefit from the 290µg Linaclotide dose. (Please refer to Section 6 of this review.)

7.2.3 Special Animal and/or In Vitro Testing

Apart from the nonclinical trials in juvenile mice, per the nonclinical reviewer, there were no special animal or in vitro tests performed. The reader is referred to section 7.2.5 below. The reader is also referred to the nonclinical review of Dr. Yuk-Chow Ng.

7.2.4 Routine Clinical Testing

Vital signs and clinical laboratory values were recorded at baseline and at each post-baseline visit in the Treatment Period, and analyzed as change from baseline to each visit for demographic subgroups. Vital sign values were potentially clinically significant (PCS) if they met both pre-specified observed value criteria and the change from baseline criteria. Clinical laboratory values were recorded at baseline and at each post-baseline visit in the Treatment Period. Laboratory values were analyzed as change from baseline at each visit. All post-baseline clinical laboratory values were assessed against pre-specified potentially clinically significant (PCS) criteria and summarized for the relevant demographic subgroups. (Please refer to the Appendix for Criteria for PCS laboratory values and vital signs.)

The following clinical laboratory evaluations were performed:

- Hematology: Absolute and differential white blood cell count, erythrocyte count, hemoglobin, hematocrit, platelet count, and red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration)
- Chemistry: Sodium, magnesium, potassium, calcium, chloride, glucose, blood urea nitrogen, creatinine, total protein, alkaline phosphatase, albumin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, bicarbonate, phosphate, uric acid, and cholesterol
- Urinalysis: Specific gravity, pH

Shift tables from baseline to end of treatment period for patients with at least one diarrhea TEAE were presented by treatment group for sodium, potassium, chloride, bicarbonate, and magnesium.

The applicant established a triplicate ECG program to assess Linaclotide prior to dosing; at post-treatment time points following a single-dose at steady state; and when clinically indicated. (Please refer to the Appendix for Criteria for PCS ECG parameters.)

The reader is referred to section 5.3.1 for detailed information on study visits and procedures. The reader is also referred to sections 5.3.2.1, 5.3.3.1, and 5.3.3.2 for specifics of the results of the individual double-blind clinical trials and to section 7.4 for integrated data.

7.2.5 Metabolic, Clearance, and Interaction Workup

Peptides are typically degraded by proteolytic enzymes in the GI tract, and thus the metabolism and degradation of Linaclotide were explained through a series of nonclinical and *in vitro* studies using the intestinal contents of rodents and humans. *In vitro* results using reconstituted intestinal fluid from human cadavers suggest that the metabolism and degradation pathway of Linaclotide and MM-419447 in humans is the same as that in the rat.

In vitro studies show that Linaclotide is not a substrate, inhibitor, or inducer of cytochrome P450 enzymes. According to the applicant, in the presence of intestinal proteases under reducing conditions *in-vitro* and in rat intestinal loops *in-vivo*, Linaclotide is rapidly degraded to short peptides and then to naturally occurring amino acids. Systemic availability of Linaclotide and its active primary metabolite, MM-419447, following oral administration in humans was below the limit of quantitation in more than 99% of all patients whose plasma was assayed. The systemic availability did not change across genders, ages, or races. There were no clinical trials specifically designed to assess drug-drug interactions. However, the applicant did perform a special safety analyses of Linaclotide co-administration with drugs commonly used in constipation and IBS-C patients. (See Section 7.2.6).

To further confirm that Linaclotide and MM-419447 were not detectable following administration of therapeutic doses of Linaclotide to patients, sparse PK sampling was conducted in the four Phase 3 efficacy trials in which patients received placebo, 145 µg of Linaclotide, or 290 µg of Linaclotide once daily for at least 12 weeks. Of the 465 Linaclotide-dosed patients whose plasma was analyzed, only two of the 313 patients receiving 290 µg Linaclotide had measurable concentrations of Linaclotide (Both were IBS-C patients and both were lower levels of quantitation (LLOQ) < 0.5 ng/mL). No patients had measurable concentrations of MM-419447 (LLOQ = 2 ng/mL).

During a fecal-recovery study in healthy subjects, only a small proportion ($\leq 6\%$ of orally administered Linaclotide was excreted as the active metabolite (MM-419447) in the feces, with a median recovery of 3 to 5%. Similar results were observed in rats. Clinical trials assessing other methods of excretion have not been conducted in humans, because of the limited systemic availability. A study in healthy and nephrectomized rats intravenously dosed with Linaclotide identified the kidney as the primary clearance organ for any active peptide in systemic circulation, with biliary clearance likely serving as a secondary pathway.

A traditional radio-labeled mass balance study was not conducted in humans. This was found to be acceptable by the clinical pharmacology reviewer and is supported by ICH S6 guidelines for peptides. Clinical trials in special populations, such as patients with renal or hepatic impairment, were not believed to be informative and therefore were not conducted. The reader is referred to the clinical pharmacology review for additional information.

The reader is also referred to Section 4 of this review for additional information.

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

As mentioned in Sections 7.2 and 7.2.4 the applicant performed specific evaluations for diarrhea, gall bladder disease, ischemic colitis, and electrolyte shifts (and consequent ECG manifestations). All these assessments are appropriate for an investigational product that is designed to be used as a laxative.

The applicant also chose to perform special evaluations of patients with certain co-morbidities making them potentially susceptible to the consequences of fluid shifts and electrolyte changes as a result of severe diarrhea. Hypertension, diabetes, and cardiovascular disorders were appropriately chosen for analysis because of their wide prevalence in the general population. TEAEs, SAEs, AEs leading to withdrawal and potentially clinically significant values for clinical laboratory parameters, vital signs, and ECG parameters were evaluated for patients with history of each of the prespecified co-morbidities.

The sponsor performed an analysis of Linaclotide safety in patients taking selected classes of medications commonly used by patients with chronic idiopathic constipation. This assessment was done to evaluate if Linaclotide, when used in combination with the selected agents, would result in clinically significant changes in clinical laboratory parameters, vital signs, or particular AEs more often than the concomitant use of these medications in patients taking placebo. The following specific agents were evaluated:

- diuretics
- agents acting on the renin-angiotensin system
- proton pump inhibitors (because of their ability to produce diarrhea and hypomagnesemia with prolonged use)
- laxatives and mineral supplements
- psychoanaleptics
- selective serotonin reuptake inhibitors
- anti-depressants

7.3 Major Safety Results

The major safety data regarding the use of Linaclotide over 12 weeks of treatment in patients with chronic idiopathic constipation participating in the Phase 3 Double-Blind Placebo-Controlled trials (Trials LIN-MD-01 and MCP-103-303) are summarized in the table below.

Table 69 Overview of Adverse Events During the 12 Week Treatment Period of the Phase 3 Double-Blind Placebo Controlled Trials in Chronic idiopathic constipation Patients

	Placebo N = 423	LIN 145µg N = 430	LIN 290µg N = 422	LIN TOTAL N = 852
	n (%)	n (%)	n (%)	n (%)
Patients with at Least 1 TEAE	222 (52.5%)	262 (60.9%)	235 (55.7%)	497 (58.3%)
Number of TEAEs	721	872	783	1655
Number of Patients in Each Category of Adverse Event				
Deaths	0	1 (0.23%)	1 (0.23%)	2 (0.23%)
Serious Adverse Event	10 (2.4%)	6 (1.4%)	11 (2.6%)	17 (2.0%)
Adverse events leading to discontinuation from trial	18 (4.3%)	34 (7.9%)	31 (7.3%)	65 (7.6%)
≥ 1 Severe TEAEs	24 (5.7%)	26 (6.0%)	31 (7.3%)	57 (6.7%)

Source: Reviewer's Table
 LIN = Linaclotide

A total of 719 patients in the combined Phase 3 double-blind, placebo-controlled trials experienced 2376 adverse events. For each of the treatment groups, at least 50% of patients experienced at least 1 TEAE. A slightly larger proportion of patients in the Linaclotide treatment arms experienced more TEAEs relative to the placebo arm. Consistent with the mechanism of action of Linaclotide, diarrhea was the most common TEAE, occurring in 15.1% of all Linaclotide treated patients and 4.7% of placebo treated patients. Of the 7 deaths that occurred during the clinical development program, 4 occurred in patients with chronic constipation. All of the deaths were considered unlikely or unrelated to study drug treatment.

7.3.1 Deaths

There were a total of 7 serious adverse events with fatal outcomes during the Linaclotide clinical development program. Of these, 6 patients were included in the safety population (i.e. took at least 1 dose of study drug). All deaths were considered to be unlikely or unrelated to study drug. Of the 6 deaths that occurred in the safety population, 4 occurred in patients with chronic idiopathic constipation (2 during the double-blind placebo-controlled trials and 2 during the long-term safety trials).

Two of the patients with chronic idiopathic constipation died from cancer (patients# 0090105 and #1033022). The first patient (#0090105) died more than 30 days (2.5 months) after stopping Linaclotide 290 µg and died of pancreatic cancer. The second patient (#1033022) was also enrolled under patient ID number 0733119. Under this patient ID the death was reported as being secondary to severe anemia and metastatic lung CA.

Patient #0160101 was also enrolled as IBS-C patient 281002 in MCP-103-202. This patient died (b) (6) after her last dose of Linaclotide 145µg as a result of intentional fentanyl toxicity.

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Patient #0093022 was taking Linaclotide 290µg and died due to multiple injuries following a fall from a ladder. Additional information on these deaths can be found in the SAE tables located in Sections 5.3.2.1, 5.3.3.1, and 5.3.3.2. A summary of all deaths in patients with chronic idiopathic constipation is provided in the table below.

Table 70 List of Chronic idiopathic constipation Patient Deaths during Linaclotide Clinical Development Program Safety Population

Study/ Patient ID	Age (years) /Sex	Days from First dose to Onset of Death ^a	Study Drug Treatment	Fatal SAE Preferred Term	Relationship to Study drug
Group 1 Phase 3 Double-Blind Placebo Controlled Chronic idiopathic constipation Trials					
LIN-MD-01 0090105	66 / F	8	Linaclotide 290µg	Pancreatic carcinoma	Unrelated
LIN-MD-01 0160101 ^b	49/ F	52	Linaclotide 145µg	Fentanyl Toxicity	Unlikely
Group 3 – Long Term Safety Trials					
MCP-103-305 ^c 1033022	48/ M	383	Linaclotide 290µg	Stage IV Esophageal CA	Unrelated
MCP-103-305 0093022	68/ M	97	Linaclotide 290µg	Multiple Injuries	Unrelated

Source: Reviewer's Table Adapted from Table 8.2-1 Applicant's Integrated Summary of Safety page 90. SAE = Serious Adverse Event

a: Day of onset/death is in relationship to date of first dose of double-blind treatment (Day 1).

b: Patient was also enrolled as IBS-C patient 281002 in MCP-103-202

c: Patient 1033022 was also enrolled under PID 0733119. The death for Patient 0733119 was reported as due to severe anemia and metastatic lung cancer

7.3.2 Nonfatal Serious Adverse Events

Additional details related to the nonfatal Serious Adverse Events (SAEs) may be found in the SAE tables located in Sections 5.3.2.1, 5.3.3.1, and 5.3.3.2. Twenty-seven patients experienced a total of 29 SAEs. A summary of the incidence of on-therapy SAEs occurring during the treatment period of the chronic idiopathic constipation trials (or within at least 30 days of the last dose of investigational product) is presented in the table below.

Table 71 Incidence of Serious Adverse Events (SAEs) for Patients with chronic idiopathic constipation During the Treatment Period of Phase 3 Double-Blind Placebo Controlled Trials or within 30 days of the last dose of Study Drug Product (Group 1) Safety Population

	Placebo N = 423	LIN145µg N = 430	LIN 290µg N = 422	LIN TOTAL N = 852
	n (%)	n (%)	n (%)	n (%)
Patients with at Least 1 SAE	10 (2.4%)	6 (1.4%)	11 (2.6%)	17 (2.0%)
Number of Patients with SAEs/100 patient-years	10.9	6.6	12.4	9.5
Selected SOCs				
<i>Preferred Terms</i>				
Cardiac disorders	3 (0.7%)	1 (0.2%)	0	1 (0.1%)
<i>Atrial Fibrillation</i>	2 (0.5%)	1 (0.2%)	0	1 (0.1%)
<i>Angina Pectoris</i>	1 (0.2%)	0	0	0
Gastrointestinal disorders	1 (0.2%)	1 (0.2%)	1 (0.2%)	2 (0.2%)
<i>Diverticulum intestinal hemorrhagic</i>	0	0	1 (0.2%)	1 (0.1%)
<i>Intestinal obstruction</i>	0	1 (0.2%)	0	1 (0.1%)
<i>Inguinal hernia</i>	1 (0.2%)	0	0	0
General disorders and administration site conditions	0	1 (0.2%)	0	1 (0.1%)
<i>Chest Pain</i>	0	1 (0.2%)	0	1 (0.1%)
Hepatobiliary disorders	1 (0.2%)	0	1 (0.2%)	1 (0.1%)
<i>Cholecystitis</i>	0	0	1 (0.2%)	1 (0.1%)
<i>Cholelithiasis</i>	1 (0.2%)	0	0	0
Infections and Infestations	4 (0.9%)	2 (0.5%)	3 (0.7%)	5 (0.6%)
<i>Bronchitis</i>	1 (0.2%)	1 (0.2%)	0	1 (0.1%)
<i>Cellulitis</i>	1 (0.2%)	0	1 (0.2%)	1 (0.1%)
<i>Diverticulitis</i>	0	0	1 (0.2%)	1 (0.1%)
<i>Pneumonia</i>	1 (0.2%)	1 (0.2%)	0	1 (0.1%)
<i>Postoperative wound infection</i>	0	0	1 (0.2%)	1 (0.1%)
<i>Viral gastroenteritis</i>	1 (0.2%)	0	0	0
Metabolism and nutrition disorders	0	0	1 (0.2%)	1 (0.1%)
<i>Dehydration</i>	0	0	1 (0.2%)	1 (0.1%)
Neoplasms, benign, malignant and unspecified	1 (0.2%)	0	2 (0.5%)	2 (0.2%)
Vascular Disorders	0	0	1 (0.2%)	1 (0.1%)
<i>Orthostatic hypotension</i>	0	0	1 (0.2%)	1 (0.1%)
Injury, Poisoning, and Procedural Complications	0	1 (0.2%)	0	1 (0.1%)
<i>Drug toxicity</i>	0	1 (0.2%)	0	1 (0.1%)
Nervous System Disorders	0	0	1 (0.2%)	1 (0.1%)
<i>Cerebrovascular disorder</i>	0	0	1 (0.2%)	1 (0.1%)

Source: Reviewer's Table Adapted from Table 5.2.1.1 of Applicants Integrated Summary of Safety pages 5764 to 5768.

LIN = Linaclotide

There were no clinically meaningful differences in the incidence of SAEs across the treatment arms. A total of 2.4% of placebo treated patients experienced an SAE. Serious adverse events were experienced by 1.4% of patients treated with Linaclotide 145µg and 2.6% of patients treated with Linaclotide 290µg. Although there were no SAEs of diarrhea, diarrhea was reported in one patient (patient #0570150 from trial LIN-MD-01 treated with Linaclotide 290µg) as a TEAE along with the SAEs of dehydration and orthostatic hypotension.

There were also 4 patients with chronic idiopathic constipation treated with Linaclotide who experienced an SAE during the Randomized Withdrawal period of Trial MCP-103-303 or during the long-term safety trial. However, the SAEs occurred within 30 days of the last dose of Linaclotide taken during the treatment period or during the treatment period of the of the lead-in trial prior to rolling into the long-term safety trial. The reader is referred to Sections 5.3.2 and 5.3.3 for additional details. The two patients in Trial MCP-103-303 were taking placebo at the time of SAE occurrence (patient #0093022 – atrial fibrillation and patient #1103005 – pulmonary embolism). The other 2 patients experienced bladder prolapse and a Spigelian hernia.

7.3.3 Dropouts and/or Discontinuations

The reader is again referred to Section 5.3 for additional information on treatment-related withdrawals. According to the applicant, more than one adverse event was allowed to be reported as a reason for a patient to withdraw from a trial. Consequently, multiple AEs may be associated with an individual patient's withdrawal. Some AEs reported at the time of a patient's withdrawal were not reported as a cause of discontinuation and do not appear as adverse events related dropouts. Therefore the following information should be interpreted with caution as it may not accurately reflect the adverse events leading to dropouts.

There were more withdrawals due to Linaclotide relative to placebo. There were 4.3% of placebo-treated patients, 7.9% of patients treated with Linaclotide 145µg, and 7.3% of patients treated with Linaclotide 290µg who discontinued from the Phase 3 trials because of an adverse event. The proportion of discontinuations was similar between both Linaclotide treatment arms. Only diarrhea and abdominal pain lead to the discontinuation of more than 1% of Linaclotide treated patients. Five of the 9 patients that withdrew because of abdominal pain also reported diarrhea. The following table summarizes the adverse events leading to trial discontinuation.

Table 72 Adverse Events leading to Trial Discontinuation of at Least 2 Linaclotide-treated Patients with chronic idiopathic constipation from the Phase 3 Double-Blind Placebo Controlled Trials (Group 1) Safety Population

Preferred Term	Number (%) of Patients			
	Placebo (N = 423)	Linaclotide		
		145 ug/day (N = 430)	290 ug/day (N = 422)	Linaclotide Total (N = 852)
Patients with AEs Leading to Withdrawal	18 (4.3)	34 (7.9)	31 (7.3)	65 (7.6)
Diarrhea	2 (0.5)	20 (4.7)	16 (3.8)	36 (4.2)
Abdominal pain	3 (0.7)	5 (1.2)	4 (0.9)	9 (1.1)
Nausea	2 (0.5)	3 (0.7)	1 (0.2)	4 (0.5)
Abdominal distension	0	3 (0.7)	0	3 (0.4)
Abdominal pain upper	0	3 (0.7)	0	3 (0.4)
Defecation urgency	0	1 (0.2)	2 (0.5)	3 (0.4)
Fecal incontinence	0	2 (0.5)	1 (0.2)	3 (0.4)
Dehydration	0	0	2 (0.5)	2 (0.2)
Dyspepsia	0	2 (0.5)	0	2 (0.2)
Flatulence	1 (0.2)	2 (0.5)	0	2 (0.2)
Headache	3 (0.7)	1 (0.2)	1 (0.2)	2 (0.2)

Source: Table 8.4.1.1-1 Applicants Integrated Summary of Safety page 105.

In addition to the adverse events leading to trial withdrawal, there were 33 patients with chronic idiopathic constipation who were lost to follow-up and 46 patients who withdrew consent. Of the 33 patients with chronic idiopathic constipation who were lost to follow-up, 1 (of 4) in the placebo arm experienced a TEAE, 2 (of 13) in the Linaclotide 145µg arm experienced a TEAE, and 3 (of 16) in the Linaclotide 290µg arm experienced a TEAE. Diarrhea was the most common ongoing TEAE at the time patients were lost to follow-up. No specific preferred term was reported in more than 1 patient in each treatment arm.

There were 46 patients with chronic idiopathic constipation in the overall safety population who withdrew consent (10 placebo, 18 Linaclotide 145µg, 18 Linaclotide 290µg). There were no differences in the number of patients who withdrew consent between the Linaclotide 145µg and 290µg doses. Both Linaclotide groups had a higher incidence of consent withdrawals relative to the placebo arm. Of the patients that withdrew consent prematurely, a higher proportion of patients in the placebo and Linaclotide 290µg treatment arms experienced at least one ongoing TEAE (3/30 placebo-treated patients, 1/18 Linaclotide 145µg-treated patients, and 3/18 Linaclotide 290µg-treated patients). There were no ongoing preferred terms for TEAEs reported more than one percent of Linaclotide treated patients. Both depression and urinary tract infection were reported in by two patients taking placebo.

7.3.4 Significant Adverse Events

Most of the adverse events reported in patients with chronic idiopathic constipation were mild to moderate in severity. Patients in the Linaclotide 290mcg group reported the largest number of severe adverse events.

Table 73 Proportion of Mild, Moderate, and Severe TEAEs by Treatment Arm Combined Chronic idiopathic constipation Phase 3 Double-Blind Placebo-Controlled Trials Safety Population

	Placebo	LIN 145µg	LIN 290 µg
Patients with at least 1 TEAE n1/N1 (%)	222/423 (52.5)	262/430 (60.9)	235/422 (55.7)
Total Number of Adverse Events in each Treatment Arm (N2)	721	872	783
Mild n2/N2 (%)	379 (52.5%)	454 (52.1%)	395 (50.4%)
Moderate n2/N2 (%)	297 (41.2%)	378 (43.3%)	329 (42.0%)
Severe n2/N2 (%)	45 (6.2%)	40 (4.6%)	58 (7.4%)
Unclassified n2/N2 (%)	0	0	1 (1.3%)

Source: Reviewers Table

N1 = Number of chronic idiopathic constipation patients in each treatment arms for Combined Phase 3 Double-Blind Placebo Controlled Trials.

n1= Number of patients in the treatment arm who experienced at least 1 TEAE

N2 = Total number of TEAEs for each treatment arm.

n2 = number of TEAEs within each category

Treatment emergent adverse events reported as severe in at least 2 Linaclotide treated patients with chronic idiopathic constipation during the Phase 3 double-blind placebo controlled trials are presented in the table below. Again, only diarrhea was reported in more than 1 % of Linaclotide-treated patients. Of the 129 Linaclotide-treated patients who experienced a diarrhea TEAE, 15 (11.6%) had events that were reported as severe. This represents approximately 1.8% of the total chronic idiopathic constipation population treated with Linaclotide during the Phase 3 double-blind placebo-controlled trials.

Table 74 Incidence of TEAEs reported as Severe Adverse Events in at least 2 Linaclotide-treated Patients with chronic idiopathic constipation During the Phase 3 Double-Blind Placebo Controlled Trials (Group 1) Safety Population

Adverse Event (Preferred Term)	Number (%) of Patients			
	Placebo (N = 423)	Linaclotide		
		145 ug/day (N = 430)	290 ug/day (N = 422)	Linaclotide Total (N = 852)
Patients with ≥ 1 severe TEAE	24 (5.7)	26 (6.0)	31 (7.3)	57 (6.7)
Diarrhea	1 (0.2)	7 (1.6)	8 (1.9)	15 (1.8)
Abdominal pain	2 (0.5)	1 (0.2)	4 (0.9)	5 (0.6)
Abdominal distension	0	1 (0.2)	3 (0.7)	4 (0.5)
Flatulence	1 (0.2)	1 (0.2)	2 (0.5)	3 (0.4)
Abdominal pain upper	1 (0.2)	2 (0.5)	0	2 (0.2)
Bronchitis	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.2)
Defecation urgency	0	0	2 (0.5)	2 (0.2)
Dyspepsia	1 (0.2)	2 (0.5)	0	2 (0.2)
Migraine	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.2)
Nausea	2 (0.5)	1 (0.2)	1 (0.2)	2 (0.2)

Source: Table 8.1.1.1.3.1-1 Applicant's Integrated Summary of Safety Volume 1 page 71.

Overall 6% of patients with chronic idiopathic constipation treated with Linaclotide 145µg, 7.3% of patients treated with Linaclotide 290µg, and 5.7% of patients treated with placebo during the Phase 3 double-blind placebo-controlled trials experienced at least 1 severe TEAE.

7.3.5 Submission Specific Primary Safety Concerns

The reader is referred to section 7.7 of this review for an assessment of ischemic colitis, diarrhea, and gallbladder disease. There is also discussion of a case of aplastic anemia. There were no additional submission specific safety concerns

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Per protocol, patients were given the opportunity to report adverse events spontaneously. In addition, at each visit following the first visit, patients were questioned (in a non-leading manner) to volunteer information regarding any AEs that had occurred since the previous visit. Examples of questions included, "Have you had any unusual signs or symptoms since your last visit?" All verbatim terms were collected on patient's eCRF. For every AE, the investigator provided the assessment of severity, causal relationship to study drug, and seriousness of the event. The investigator was also permitted to allow a patient to temporarily interrupt study drug (one time only) for up to three days should an AE occur. Adverse events were also detected through physical examination, laboratory tests or other assessments.

Using the JMP statistical software and adverse events analysis dataset for Trials LIN-MD-01 and MCP-103-303 combined, the clinical reviewer verified the most common treatment emergent adverse events (TEAEs) in the safety population. Information requests were generated when there were discrepancies between the reviewer and applicant analyses. Discrepancies occurred infrequently and were minor (1 or 2 patients). In most cases the differences in numbers could be explained by the use of different variables during the performance of an analysis or the presence of duplicate patients in the datasets. (See Section 7.1.1) At times minor discrepancies were due to inclusion of patients from the Randomized-Withdrawal period of trial MCP-103-303 into analyses that were intended to evaluate the Treatment Period only.

The applicant proposed to include in labeling those adverse events that occurred in greater than 2% of the population and occurring at a greater incidence in the Linaclotide treated group relative to the placebo group. The treatment emergent adverse events (TEAEs) experienced by at least 2% of all Linaclotide patients in the Phase 3 Double Blind trials and at an incidence of at least 1% more than placebo patients were diarrhea (15.1% vs. 4.7%), abdominal pain (4.2% vs. 3.1%), and abdominal distension (3.5% vs. 2.4%). There was some splitting of the preferred terms that may represent abdominal pain. When the clinical reviewer combined the preferred terms "abdominal pain", "upper abdominal pain" and "lower abdominal pain" into one group, the incidence was 6% in placebo treated patients, 7% in patients treated with Linaclotide 145µg and 6% in patients treated with Linaclotide 290µg. It is possible that this incidence would have been higher if abdominal discomfort was also included in the analysis.

When the clinical reviewer lowered the AE threshold to 1%, it was discovered that 1.3% of patients in the Linaclotide 145µg group experienced fecal incontinence as opposed to 0% in the placebo group and 0.5% in the Linaclotide 290µg group. The most common adverse events are presented by preferred term in the table below.

Table 75 Treatment Emergent Adverse Events Reported in >1% of Patients in Any Treatment Group of the Pooled CIC Phase 3 Double-Blind Placebo Controlled Trials - Safety Population

Number of Patients with Adverse Event (Preferred Term)	Number (%) of Patients			
	Placebo (N = 423) n(%)	Linaclotide		
		145µg/day (N = 430) N(%)	290µg/day (N = 422) n(%)	Linaclotide Total (N = 852) n(%)
Number of Patients with Any TEAE	222 (52.5%)	262 (60.9%)	235 (55.7%)	497 (58.3%)
Diarrhoea	19 (4.5%)	69 (16.0%)	60 (14.2%)	129 (15.1%)
Flatulence	21 (4.9%)	24 (5.6%)	21 (5.0%)	45 (5.3%)
Upper respiratory tract infection	17 (4.0%)	22 (5.1%)	14 (3.3%)	36 (4.2)
Headache	19 (4.5%)	15 (3.5%)	18 (4.3%)	33 (3.9%)
Nausea	16 (3.7%)	16 (3.7%)	19 (4.5%)	35 (4.1%)
Abdominal pain	13 (3.1%)	16 (3.7%)	20 (4.7%)	36 (4.2%)
Urinary tract infection	15 (3.5%)	18 (4.2%)	12 (2.8%)	30 (3.5%)
Nasopharyngitis	14 (3.3%)	9 (2.1%)	17 (4.0%)	26 (3.1%)
Abdominal distension	9 (2.1%)	16 (3.7%)	15 (3.6%)	31 (3.6%)
Sinusitis	8 (1.9%)	15 (3.5%)	11 (2.6%)	26 (3.1%)
Back pain	10 (2.4%)	7 (1.6%)	8 (1.9%)	15 (1.8%)
Vomiting	9 (2.1%)	5 (1.2%)	10 (2.4%)	15 (1.8%)
Abdominal pain upper	6 (1.4%)	13 (3.0%)	5 (1.2%)	18 (2.1%)
Bronchitis	9 (2.1%)	5 (1.2%)	4 (0.9%)	9 (1.1%)
Dyspepsia	3 (0.7%)	8 (1.9%)	3 (0.7%)	11 (1.3%)
Gastroenteritis viral	4 (0.9%)	8 (1.9%)	2 (0.5%)	10 (1.2%)
Oropharyngeal pain	6 (1.4%)	6 (1.4%)	2 (0.5%)	8 (0.9%)
Dizziness	2 (0.5%)	4 (0.9%)	7 (1.7%)	11 (1.3%)
Sinus congestion	5 (1.2%)	1 (0.2%)	7 (1.7%)	8 (0.9%)
Cough	4 (0.9%)	7 (1.6%)	2 (0.5%)	9 (1.1%)
Influenza	2 (0.5%)	7 (1.6%)	2 (0.5%)	9 (1.1%)
Arthralgia	3 (0.7%)	1 (0.2%)	6 (1.4%)	7 (0.8%)
Fatigue	2 (0.5%)	6 (1.4%)	2 (0.5%)	8 (0.9%)
Gastroesophageal reflux disease	2 (0.5%)	2 (0.5%)	5 (1.2%)	7 (0.8%)
Faecal incontinence	1 (0.2%)	6 (1.4%)	2 (0.5%)	8 (0.9%)
Muscle strain	2 (0.5%)	5 (1.2%)	2 (0.5%)	7 (0.8%)
Gastrointestinal sounds abnormal	0	2 (0.5%)	5 (1.2%)	7 (0.8%)
Depression	5 (1.2%)	2 (0.5%)	0	2 (0.2%)

Source: Reviewer's Table generated from combined ADAE and ADSL

Approximately 56% (719/1275) of patients in the CIC Phase 3 Double Blind trials (Group 1) experienced at least one Treatment Emergent Adverse Event (TEAE). Patients in the Linaclotide treatment groups experienced more TEAEs (60.9% in the Linaclotide 145µg arm, 55.7% in the 290µg arm) than patients randomized to receive placebo (52.2%). The most frequently reported TEAEs were from the "Gastrointestinal disorders" and "Infections and Infestations" system organ class (SOC). Diarrhea was the most commonly reported adverse event occurring in 16% of patients treated with Linaclotide 145µg, 14.2% of patients treated with Linaclotide 290µg and 4.5% of patients treated with placebo. This is consistent with the pharmacology of the proposed product. If the pharmacodynamic outcome is directly

proportional to receptor occupancy and dose (as suggested by the Phase 2 dose ranging trials), it is unclear why patients taking the lower dose of Linaclotide would experience more diarrhea than those taking the higher dose. One would expect that patients taking the higher dose would experience more diarrhea. However, this finding is somewhat consistent with the contradictory results for the primary efficacy variable in the 2 Phase 3 Double-Blind trials, which suggest that the 290µg dose offers no greater efficacy over placebo than the 145µg dose.

For TEAEs that occurred in < 2% of patients taking either dose of Linaclotide and at an incidence greater than placebo, the difference between Linaclotide and placebo was < 1% for all AEs except: faecal incontinence (Linaclotide 145 µg, 1.4% vs. placebo 0.2%); dyspepsia (Linaclotide 145 µg, 1.9% vs. placebo 0.7%); viral gastroenteritis (Linaclotide 145 µg, 1.9% vs. placebo 0.9%); abnormal gastrointestinal sounds (Linaclotide 290 µg, 1.2% vs. placebo 0%); influenza (Linaclotide 145µg 1.6% vs. placebo 0.5%) and dizziness (Linaclotide 1.7% vs. placebo 0.5%). Based on the information that is provided it not possible to determine if the any of the dizziness was attributable to dehydration.

7.4.2 Laboratory Findings

Additional details related to the laboratory findings for the individual double-blind placebo control trials submitted in support of the chronic idiopathic constipation indication may be found in Sections 5.3.2.1, 5.3.3.1, and 5.3.3.2 of this review.

Descriptive statistics were used to describe changes from baseline in laboratory findings and laboratory parameters at baseline, at each post baseline visit, and at the end of treatment period. The applicant provided summary statistics for hematology values, blood chemistries, and urinalyses. The applicant also presented shifts in laboratory value findings, potentially clinically significant values, and values reported as TEAEs.

There were no clinically meaningful differences in mean values between placebo and both Linaclotide treatment groups. Changes from baseline to the end of the Treatment period were also inconsequential and not clinically meaningful among the three treatment arms. Over 95% of patients with chronic idiopathic constipation across each of the treatment arms had normal baseline values that remained normal at the end of the treatment period for absolute basophil count, absolute eosinophil account, hematocrit, hemoglobin, absolute lymphocyte count, mean corpuscular hemoglobin, mean corpuscular volume, absolute monocyte count, absolute neutrophil count, platelet count, white blood cell count, and red blood cell count.

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Table 76 Shift from Baseline to End of Treatment for Hematology Parameters in Chronic idiopathic constipation Patients Double-Blind Placebo Controlled Trial (Group 1) Safety Population

Lab Parameter (Unit): Basophils Absolute Cell Count (10**9/L)

		CC			
Baseline	End of TP	Placebo (N=423) n/N1 (%)	LIN 145 (N=430) n/N1 (%)	LIN 290 (N=422) n/N1 (%)	LIN Total (N=852) n/N1 (%)
Low	Low	0	0	0	0
Low	Normal	0	0	0	0
Low	High	0	0	0	0
Normal	Low	0/417	0/421	0/411	0/832
Normal	Normal	415/417 (99.5)	419/421 (99.5)	409/411 (99.5)	828/832 (99.5)
Normal	High	2/417 (0.5)	2/421 (0.5)	2/411 (0.5)	4/832 (0.5)
High	Low	0/ 2	0/ 2	0/ 1	0/ 3
High	Normal	2/ 2 (100)	2/ 2 (100)	1/ 1 (100)	3/ 3 (100)
High	High	0/ 2	0/ 2	0/ 1	0/ 3

Lab Parameter (Unit): Eosinophils Absolute Cell Count (10**9/L)

		CC			
Baseline	End of TP	Placebo (N=423) n/N1 (%)	LIN 145 (N=430) n/N1 (%)	LIN 290 (N=422) n/N1 (%)	LIN Total (N=852) n/N1 (%)
Low	Low	0	0	0	0
Low	Normal	0	0	0	0
Low	High	0	0	0	0
Normal	Low	0/410	0/419	0/406	0/825
Normal	Normal	405/410 (98.8)	419/419 (100)	406/406 (100)	825/825 (100)
Normal	High	5/410 (1.2)	0/419	0/406	0/825
High	Low	0/ 9	0/ 4	0/ 6	0/ 10
High	Normal	5/ 9 (55.6)	3/ 4 (75.0)	3/ 6 (50.0)	6/ 10 (60.0)
High	High	4/ 9 (44.4)	1/ 4 (25.0)	3/ 6 (50.0)	4/ 10 (40.0)

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Lab Parameter (Unit): Hematocrit (RATIO)

		CC			
Baseline	End of TP	Placebo (N=423) n/N1 (%)	LIN 145 (N=430) n/N1 (%)	LIN 290 (N=422) n/N1 (%)	LIN Total (N=852) n/N1 (%)
Low	Low	12/ 30 (40.0)	9/ 25 (36.0)	15/ 33 (45.5)	24/ 58 (41.4)
Low	Normal	18/ 30 (60.0)	16/ 25 (64.0)	18/ 33 (54.5)	34/ 58 (58.6)
Low	High	0/ 30	0/ 25	0/ 33	0/ 58
Normal	Low	11/386 (2.8)	8/397 (2.0)	16/377 (4.2)	24/774 (3.1)
Normal	Normal	370/386 (95.9)	383/397 (96.5)	356/377 (94.4)	739/774 (95.5)
Normal	High	5/386 (1.3)	6/397 (1.5)	5/377 (1.3)	11/774 (1.4)
High	Low	0/ 3	0/ 1	0/ 2	0/ 3
High	Normal	3/ 3 (100)	0/ 1	2/ 2 (100)	2/ 3 (66.7)
High	High	0/ 3	1/ 1 (100)	0/ 2	1/ 3 (33.3)

Lab Parameter (Unit): Hemoglobin (G/L)

		CC			
Baseline	End of TP	Placebo (N=423) n/N1 (%)	LIN 145 (N=430) n/N1 (%)	LIN 290 (N=422) n/N1 (%)	LIN Total (N=852) n/N1 (%)
Low	Low	23/ 29 (79.3)	10/ 22 (45.5)	25/ 36 (69.4)	35/ 58 (60.3)
Low	Normal	6/ 29 (20.7)	12/ 22 (54.5)	11/ 36 (30.6)	23/ 58 (39.7)
Low	High	0/ 29	0/ 22	0/ 36	0/ 58
Normal	Low	11/384 (2.9)	12/397 (3.0)	17/373 (4.6)	29/770 (3.8)
Normal	Normal	371/384 (96.6)	385/397 (97.0)	354/373 (94.9)	739/770 (96.0)
Normal	High	2/384 (0.5)	0/397	2/373 (0.5)	2/770 (0.3)
High	Low	0/ 6	0/ 4	0/ 3	0/ 7
High	Normal	6/ 6 (100)	2/ 4 (50.0)	3/ 3 (100)	5/ 7 (71.4)
High	High	0/ 6	2/ 4 (50.0)	0/ 3	2/ 7 (28.6)

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Lab Parameter (Unit): Lymphocytes Absolute Cell Count (10**9/L)

		CC			
Baseline	End of TP	Placebo (N=423) n/N1 (%)	LIN 145 (N=430) n/N1 (%)	LIN 290 (N=422) n/N1 (%)	LIN Total (N=852) n/N1 (%)
Low	Low	11/ 16 (68.8)	13/ 26 (50.0)	13/ 23 (56.5)	26/ 49 (53.1)
Low	Normal	5/ 16 (31.3)	13/ 26 (50.0)	10/ 23 (43.5)	23/ 49 (46.9)
Low	High	0/ 16	0/ 26	0/ 23	0/ 49
Normal	Low	12/398 (3.0)	12/391 (3.1)	16/388 (4.1)	28/779 (3.6)
Normal	Normal	384/398 (96.6)	378/391 (96.7)	371/388 (95.6)	749/779 (96.1)
Normal	High	2/398 (0.5)	1/391 (0.3)	1/388 (0.3)	2/779 (0.3)
High	Low	0/ 5	0/ 6	0/ 1	0/ 7
High	Normal	5/ 5 (100)	3/ 6 (50.0)	0/ 1	3/ 7 (42.9)
High	High	0/ 5	3/ 6 (50.0)	1/ 1 (100)	4/ 7 (57.1)

Lab Parameter (Unit): Monocytes Absolute Cell Count (10**9/L)

		CC			
Baseline	End of TP	Placebo (N=423) n/N1 (%)	LIN 145 (N=430) n/N1 (%)	LIN 290 (N=422) n/N1 (%)	LIN Total (N=852) n/N1 (%)
Low	Low	0	0	0	0
Low	Normal	0	0	0	0
Low	High	0	0	0	0
Normal	Low	0/417	0/422	0/409	0/831
Normal	Normal	407/417 (97.6)	415/422 (98.3)	404/409 (98.8)	819/831 (98.6)
Normal	High	10/417 (2.4)	7/422 (1.7)	5/409 (1.2)	12/831 (1.4)
High	Low	0/ 2	0/ 1	0/ 3	0/ 4
High	Normal	1/ 2 (50.0)	1/ 1 (100)	3/ 3 (100)	4/ 4 (100)
High	High	1/ 2 (50.0)	0/ 1	0/ 3	0/ 4

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Lab Parameter (Unit): Neutrophils Absolute Cell Count (10**9/L)

		CC			
Baseline	End of TP	Placebo (N=423) n/N1 (%)	LIN 145 (N=430) n/N1 (%)	LIN 290 (N=422) n/N1 (%)	LIN Total (N=852) n/N1 (%)
Low	Low	8/ 16 (50.0)	5/ 12 (41.7)	3/ 8 (37.5)	8/ 20 (40.0)
Low	Normal	7/ 16 (43.8)	7/ 12 (58.3)	5/ 8 (62.5)	12/ 20 (60.0)
Low	High	1/ 16 (6.3)	0/ 12	0/ 8	0/ 20
Normal	Low	6/388 (1.5)	9/396 (2.3)	5/392 (1.3)	14/788 (1.8)
Normal	Normal	373/388 (96.1)	382/396 (96.5)	378/392 (96.4)	760/788 (96.4)
Normal	High	9/388 (2.3)	5/396 (1.3)	9/392 (2.3)	14/788 (1.8)
High	Low	0/ 15	0/ 15	0/ 12	0/ 27
High	Normal	12/ 15 (80.0)	11/ 15 (73.3)	10/ 12 (83.3)	21/ 27 (77.8)
High	High	3/ 15 (20.0)	4/ 15 (26.7)	2/ 12 (16.7)	6/ 27 (22.2)

Lab Parameter (Unit): Platelet Count (Thrombocytes) (10**9/L)

		CC			
Baseline	End of TP	Placebo (N=423) n/N1 (%)	LIN 145 (N=430) n/N1 (%)	LIN 290 (N=422) n/N1 (%)	LIN Total (N=852) n/N1 (%)
Low	Low	1/ 1 (100)	2/ 3 (66.7)	0/ 1	2/ 4 (50.0)
Low	Normal	0/ 1	1/ 3 (33.3)	1/ 1 (100)	2/ 4 (50.0)
Low	High	0/ 1	0/ 3	0/ 1	0/ 4
Normal	Low	0/372	2/372 (0.5)	0/367	2/739 (0.3)
Normal	Normal	363/372 (97.6)	359/372 (96.5)	356/367 (97.0)	715/739 (96.8)
Normal	High	9/372 (2.4)	11/372 (3.0)	11/367 (3.0)	22/739 (3.0)
High	Low	0/ 46	0/ 46	0/ 44	0/ 90
High	Normal	21/ 46 (45.7)	25/ 46 (54.3)	23/ 44 (52.3)	48/ 90 (53.3)
High	High	25/ 46 (54.3)	21/ 46 (45.7)	21/ 44 (47.7)	42/ 90 (46.7)

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Lab Parameter (Unit): Red Blood Cell Count (10**12/L)

		CC			
Baseline	End of TP	Placebo (N=423) n/N1 (%)	LIN 145 (N=430) n/N1 (%)	LIN 290 (N=422) n/N1 (%)	LIN Total (N=852) n/N1 (%)
Low	Low	7/ 14 (50.0)	10/ 17 (58.8)	11/ 18 (61.1)	21/ 35 (60.0)
Low	Normal	7/ 14 (50.0)	7/ 17 (41.2)	7/ 18 (38.9)	14/ 35 (40.0)
Low	High	0/ 14	0/ 17	0/ 18	0/ 35
Normal	Low	7/402 (1.7)	10/400 (2.5)	13/391 (3.3)	23/791 (2.9)
Normal	Normal	394/402 (98.0)	389/400 (97.3)	376/391 (96.2)	765/791 (96.7)
Normal	High	1/402 (0.2)	1/400 (0.3)	2/391 (0.5)	3/791 (0.4)
High	Low	0/ 3	0/ 6	0/ 3	0/ 9
High	Normal	3/ 3 (100)	2/ 6 (33.3)	1/ 3 (33.3)	3/ 9 (33.3)
High	High	0/ 3	4/ 6 (66.7)	2/ 3 (66.7)	6/ 9 (66.7)

Lab Parameter (Unit): White Blood Cell Count (10**9/L)

		CC			
Baseline	End of TP	Placebo (N=423) n/N1 (%)	LIN 145 (N=430) n/N1 (%)	LIN 290 (N=422) n/N1 (%)	LIN Total (N=852) n/N1 (%)
Low	Low	6/ 10 (60.0)	7/ 9 (77.8)	2/ 6 (33.3)	9/ 15 (60.0)
Low	Normal	4/ 10 (40.0)	2/ 9 (22.2)	4/ 6 (66.7)	6/ 15 (40.0)
Low	High	0/ 10	0/ 9	0/ 6	0/ 15
Normal	Low	6/398 (1.5)	7/406 (1.7)	6/398 (1.5)	13/804 (1.6)
Normal	Normal	389/398 (97.7)	393/406 (96.8)	384/398 (96.5)	777/804 (96.6)
Normal	High	3/398 (0.8)	6/406 (1.5)	8/398 (2.0)	14/804 (1.7)
High	Low	0/ 11	0/ 8	0/ 8	0/ 16
High	Normal	7/ 11 (63.6)	6/ 8 (75.0)	8/ 8 (100)	14/ 16 (87.5)
High	High	4/ 11 (36.4)	2/ 8 (25.0)	0/ 8	2/ 16 (12.5)

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Lab Parameter (Unit): Mean Corpuscular Volume (FL)

		CC			
Baseline	End of TP	Placebo (N=423) n/N1 (%)	LIN 145 (N=430) n/N1 (%)	LIN 290 (N=422) n/N1 (%)	LIN Total (N=852) n/N1 (%)
Low	Low	10/ 15 (66.7)	9/ 14 (64.3)	14/ 21 (66.7)	23/ 35 (65.7)
Low	Normal	5/ 15 (33.3)	5/ 14 (35.7)	7/ 21 (33.3)	12/ 35 (34.3)
Low	High	0/ 15	0/ 14	0/ 21	0/ 35
Normal	Low	3/404 (0.7)	0/407	0/389	0/796
Normal	Normal	399/404 (98.8)	402/407 (98.8)	387/389 (99.5)	789/796 (99.1)
Normal	High	2/404 (0.5)	5/407 (1.2)	2/389 (0.5)	7/796 (0.9)
High	Low	0	0/ 2	0/ 2	0/ 4
High	Normal	0	0/ 2	0/ 2	0/ 4
High	High	0	2/ 2 (100)	2/ 2 (100)	4/ 4 (100)

Source: Applicant's After-text Table 7.6.1.2 Volume 2 Integrated Summary of Safety pages 10906 – 10918.

N = number of Chronic idiopathic constipation patients in the Safety Population for the Treatment Group

N1 = number of patients with a non-missing baseline and end-of-treatment value in the specific baseline category.

n = number of patients in the shift category.

Baseline is defined as the last assessment prior to the first dose of double-blind study drug treatment in the treatment period.

End of TP (treatment period) is defined as the last nonmissing values in the treatment period following the date of the first dose of double-blind study drug of the treatment period.

Criteria for potentially clinically significant laboratory assessments are presented in Appendix 9.4. The incidence of potentially clinically significant hematology values was generally low and similar across treatment group. The only parameter for which potentially clinically significant values were reported in $\geq 2\%$ of patients with chronic idiopathic constipation in any treatment group was low lymphocyte count. A larger proportion of patients in the Linaclotide treatment groups had low absolute lymphocyte counts post-baseline relative to the placebo treatment group (2.5% Linaclotide 145 μg group, 2.5% Linaclotide 290 μg group, and 1.4% placebo). In addition over 1% of patients across all treatment groups had a potentially clinically significant decrease post-baseline value for the absolute neutrophil count (1.9% for placebo, 1.4% for Linaclotide 145 μg , and 1.7% for Linaclotide 290 μg). The similarities across all treatment arms in the proportions patients with low absolute neutrophil counts is somewhat reassuring, and suggests that this observation is unlikely to be study-drug related. Stimulation of guanylate cyclase-c receptors by uroguanylin agonists increases the intracellular production of cGMP signaling a cascade that results in down-regulation of inflammatory cytokines. The observed changes in absolute lymphocyte count may reflect the anti-inflammatory potential of this product.²² The reader is also referred to Section 7.6.1 of this review. The number of patients experiencing potential clinically significant changes in laboratory values after baseline is presented in the table below.

Table 77 Incidence of Post-baseline Potentially Clinically Significant Laboratory Parameter Values During the Treatment Period of Double-Blind Placebo Controlled Trials for Chronic idiopathic constipation (Group 1) Safety Population

Clinical Laboratory Group Parameter (Unit) PCS Criterion	CC			
	Placebo (N=423) n/N1 (%)	LIN 145 (N=430) n/N1 (%)	LIN 290 (N=422) n/N1 (%)	LIN Total (N=852) n/N1 (%)
Hematology				
Basophils Absolute Cell Count (10**9/L)				
> 3 * ULN	0/ 419	0/ 423	0/ 412	0/ 835
Eosinophils Absolute Cell Count (10**9/L)				
> 3 * ULN	0/ 418	0/ 423	0/ 412	0/ 835
Hematocrit (RATIO)				
< 0.9 * LLN	2/ 415 (0.5)	1/ 422 (0.2)	1/ 410 (0.2)	2/ 832 (0.2)
> 1.1 * ULN	0/ 415	0/ 422	0/ 410	0/ 832
Hemoglobin (G/L)				
< 0.9 * LLN	5/ 414 (1.2)	2/ 422 (0.5)	4/ 408 (1.0)	6/ 830 (0.7)
> 1.1 * ULN	0/ 414	1/ 422 (0.2)	0/ 408	1/ 830 (0.1)
Lymphocytes Absolute Cell Count (10**9/L)				
< 0.8 * LLN	6/ 414 (1.4)	11/ 422 (2.6)	10/ 406 (2.5)	21/ 828 (2.5)
> 1.5 * ULN	0/ 414	1/ 422 (0.2)	0/ 406	1/ 828 (0.1)
Mean Corpuscular Hemoglobin (PG)				
> 3 * ULN	0/ 419	0/ 423	0/ 412	0/ 835
Mean Corpuscular Hemoglobin Conc. (G/L)				
> 3 * ULN	0/ 419	0/ 423	0/ 412	0/ 835
Mean Corpuscular Volume (FL)				
< 0.9 * LLN	0/ 419	0/ 422	1/ 406 (0.2)	1/ 828 (0.1)
> 1.1 * ULN	0/ 419	0/ 422	0/ 406	0/ 828
Monocytes Absolute Cell Count (10**9/L)				
> 3 * ULN	0/ 419	0/ 423	0/ 412	0/ 835
Neutrophils Absolute Cell Count (10**9/L)				
< 0.8 * LLN	8/ 412 (1.9)	6/ 418 (1.4)	7/ 406 (1.7)	13/ 824 (1.6)
> 1.5 * ULN	0/ 412	3/ 418 (0.7)	5/ 406 (1.2)	8/ 824 (1.0)
Platelet Count (Thrombocytes) (10**9/L)				
< 0.5 * LLN	0/ 419	1/ 421 (0.2)	0/ 409	1/ 830 (0.1)
> 1.5 * ULN	0/ 419	1/ 421 (0.2)	0/ 409	1/ 830 (0.1)
Red Blood Cell Count (10**12/L)				
< 0.9 * LLN	1/ 419 (0.2)	1/ 423 (0.2)	2/ 410 (0.5)	3/ 833 (0.4)
> 1.1 * ULN	0/ 419	1/ 423 (0.2)	1/ 410 (0.2)	2/ 833 (0.2)
White Blood Cell Count (10**9/L)				
< 0.7 * LLN	1/ 418 (0.2)	1/ 422 (0.2)	0/ 412	1/ 834 (0.1)
> 1.5 * ULN	0/ 418	1/ 422 (0.2)	0/ 412	1/ 834 (0.1)

Source: Table 7.2.1. Applicants Integrated Summary of Safety Volume 2 pages 7183 – 7184.

PCS = Potentially Clinically Significant, LLN = Lower Limit of Normal, ULN = upper limit of normal.

N = number of patients in a specific treatment group, N1 = Number of patients with a non-PCS baseline and at least one nonmissing postbaseline value during the double-blind treatment period.

n = number of patients with a non-PCS baseline and at least one PCS baseline value during the double-blind treatment period.

There were no clinically meaningful differences in mean values for blood chemistries between the placebo and Linaclotide treatment group. Changes from baseline were unremarkable. Approximately 95% or more patients across all treatment arms had baseline normal values that remained normal at the end of the treatment period for SGPT, SGOT, Albumin, Alkaline Phosphatase, Bicarbonate, Chloride, Total Bilirubin, Creatinine, Magnesium, Phosphorus, Potassium, Sodium, and total protein. In the patients with chronic idiopathic constipation, 1.7% of the patients treated with Linaclotide 290 μ g, 1.4% of the patients treated with Linaclotide 145 μ g, and 0.7% of placebo-treated patients had a shift in Bicarbonate from normal at baseline to low at least once during the treatment period. In most cases Bicarbonate levels returned to normal range by the end of the treatment period.

There were no remarkable differences across treatment groups for chemistry values reported as treatment emergent adverse events. There were no chemistry-related treatment emergent adverse events reported in $\geq 1\%$ of patients with chronic idiopathic constipation. Three Linaclotide-treated patients with chronic idiopathic constipation discontinued from a trial because of abnormal chemistry results. Patient #0060102 had hyponatremia but did not experienced a diarrhea TEAE. Patient #223004 had an increased blood glucose value and hypothyroidism and hepatic enzyme increased was reported patient #0310125.

Potentially clinically significant criteria for blood chemistries are also presented in Appendix 9.4. The incidence of potentially clinically significant chemistry values was similar across of all treatment groups and less than 2% for each parameter. The incidence of potentially clinically significant laboratory parameters is presented in the table below.

Table 78 Incidence of Postbaseline Potentially Clinically Significant Laboratory Parameters During Treatment Period Chronic idiopathic constipation Phase 3 Double-Blind Placebo-Controlled Trials Safety Population (Group 1)

Clinical Laboratory Group Parameter (Unit) PCS Criterion	Placebo (N=423) n/N1 (%)	LIN 145 (N=430) n/N1 (%)	LIN 290 (N=422) n/N1 (%)	LIN Total (N=852) n/N1 (%)
Chemistry				
Alanine Aminotransferase (SGPT) (U/L)				
>= 3 * ULN	0/ 419	0/ 422	2/ 411 (0.5)	2/ 833 (0.2)
Albumin (G/L)				
< 0.9 * LLN	1/ 418 (0.2)	0/ 423	2/ 410 (0.5)	2/ 833 (0.2)
> 1.1 * ULN	1/ 418 (0.2)	1/ 423 (0.2)	0/ 410	1/ 833 (0.1)
Alkaline Phosphatase (U/L)				
>= 3 * ULN	0/ 419	0/ 423	0/ 411	0/ 834
Aspartate Aminotransferase (SGOT) (U/L)				
>= 3 * ULN	2/ 419 (0.5)	1/ 423 (0.2)	1/ 411 (0.2)	2/ 834 (0.2)
Bicarbonate (HCO3) (MMOL/L)				
< 0.9 * LLN	1/ 419 (0.2)	0/ 423	1/ 411 (0.2)	1/ 834 (0.1)
> 1.1 * ULN	0/ 419	0/ 423	0/ 411	0/ 834
Bilirubin, Total (UMOL/L)				
> 1.5 * ULN	2/ 419 (0.5)	1/ 420 (0.2)	0/ 412	1/ 832 (0.1)
Blood Urea Nitrogen (MMOL/L)				
> 1.2 * ULN	5/ 418 (1.2)	1/ 422 (0.2)	4/ 411 (1.0)	5/ 833 (0.6)
Calcium (MMOL/L)				
< 0.9 * LLN	0/ 418	0/ 422	0/ 412	0/ 834
> 1.1 * ULN	1/ 418 (0.2)	0/ 422	0/ 412	0/ 834
Chloride (MMOL/L)				
< 0.9 * LLN	0/ 419	0/ 423	0/ 412	0/ 835
> 1.1 * ULN	0/ 419	0/ 423	0/ 412	0/ 835
Cholesterol, Total (MMOL/L)				
> 1.6 * ULN	2/ 417 (0.5)	1/ 417 (0.2)	1/ 409 (0.2)	2/ 826 (0.2)
Creatinine (UMOL/L)				
> 1.3 * ULN	3/ 417 (0.7)	1/ 422 (0.2)	2/ 411 (0.5)	3/ 833 (0.4)
Glucose, Non-fasting (MMOL/L)				
< 0.8 * LLN	6/ 412 (1.5)	5/ 420 (1.2)	2/ 408 (0.5)	7/ 828 (0.8)
> 1.4 * ULN	6/ 412 (1.5)	1/ 420 (0.2)	4/ 408 (1.0)	5/ 828 (0.6)
Magnesium (MMOL/L)				
< 0.9 * LLN	0/ 418	1/ 422 (0.2)	0/ 411	1/ 833 (0.1)
> 1.1 * ULN	0/ 418	0/ 422	0/ 411	0/ 833
Phosphorus (MMOL/L)				
< 0.9 * LLN	4/ 418 (1.0)	4/ 421 (1.0)	2/ 406 (0.5)	6/ 827 (0.7)
> 1.1 * ULN	4/ 418 (1.0)	3/ 421 (0.7)	3/ 406 (0.7)	6/ 827 (0.7)
Potassium (MMOL/L)				
< 0.9 * LLN	2/ 413 (0.5)	2/ 416 (0.5)	3/ 408 (0.7)	5/ 824 (0.6)
> 1.1 * ULN	1/ 413 (0.2)	2/ 416 (0.5)	1/ 408 (0.2)	3/ 824 (0.4)
Protein, Total (G/L)				
< 0.9 * LLN	0/ 419	0/ 421	1/ 412 (0.2)	1/ 833 (0.1)
> 1.1 * ULN	1/ 419 (0.2)	0/ 421	0/ 412	0/ 833
Sodium (MMOL/L)				
< 0.9 * LLN	0/ 419	0/ 423	0/ 412	0/ 835
> 1.1 * ULN	0/ 419	0/ 423	0/ 412	0/ 835
Uric Acid (Urate) (UMOL/L)				
< 0.9 * LLN	0/ 0	0/ 0	0/ 0	0/ 0
> 1.1 * ULN	0/ 0	0/ 0	0/ 0	0/ 0

Source: Table 7.2.1 Applicants Integrated Summary of Safety Volume 2 pages 7184 – 7186

LLN = Lower Limit of Normal ULN = Upper Limit of Normal

N = number of patients in the specific treatment group. N1 = number of patients with a non-PCS baseline and at least one nonmissing postbaseline value during the double-blind treatment period.

n = number of patients with a non-PCS baseline and at least one PCS postbaseline value during the double-blind treatment period

Assessment of urinalysis values were negative for a potential safety issue. There were no clinically meaningful differences across the treatment groups for the urinalysis parameter and there were no values classified as potentially clinically significant. There were no differences in the incidence of TEAEs, SAEs, or early withdrawals across treatment groups for urinalysis values.

7.4.3 Vital Signs

Descriptive statistics of the actual value and change from baseline value at each of the post-baseline visits and at the End of the Treatment Period were presented by the applicant. Vital sign trends, individual potentially clinically significant abnormalities, and changes over time were reviewed. A slightly higher proportion of patients in the Linaclotide 290µg group experienced changes in diastolic blood pressure relative to the other treatment groups. There were no clinically meaningful changes or differences among the treatment arms of the double-blind placebo-controlled trials for chronic idiopathic constipation. With the exception of weight, no vital sign parameter was reported as potentially clinically significant in ≥2 % of patients in any treatment group. Changes in weight were similar across treatment groups and there were no remarkable differences in the proportion of patient that had an increase or decrease in body weight by 7% or more. The number of patients with potentially clinically significant vital sign changes is presented in the table below.

Table 79 Number (%) of Chronic idiopathic constipation Patients with Potentially Clinically Significant Vital Sign Values During the Treatment Period of the Phase 3 Double Blind Placebo-Controlled Trials (Group 1) Safety Population

		Linaclotide	
		145 ug/day (N=430)	290 ug/day (N=422)
Vital Sign	Potentially Clinically Significant Criteria	n/N1 (%)	n/N1 (%)
Systolic BP, mm Hg	≤ 90 and decrease ≥ 20	7/426 (1.6)	3/417 (0.7)
	≥ 180 and increase ≥ 20	0/426	0/417
Diastolic BP, mm Hg	≤ 50 and decrease ≥ 15	1/426 (0.2)	4/417 (1.0)
	≥ 105 and increase ≥ 15	0/426	2/417 (0.5)
Pulse rate, bpm	≤ 50 and decrease ≥ 15	2/427 (0.5)	2/417 (0.5)
	≥ 120 and increase ≥ 15	0/427	0/417
Weight, kg	Decrease ≥ 7%	8/427 (1.9)	9/417 (2.2)
	Increase ≥ 7%	6/427 (1.4)	7/417 (1.7)

Source: Applicants Integrated Summary of Safety page 148 Table 10.1.1.2-1

Only parameters for patients who had at least 1 PCS postbaseline value (high or low) are included.

BP = Blood Pressure.

N1 = number of patients with non-PCS baseline values and at least 1 nonmissing postbaseline value;

n = number of patients with non-PCS baseline values and at least 1 PCS postbaseline value; PCS = potentially clinically significant

7.4.4 Electrocardiograms (ECGs)

The reader is referred to Section 5.3.3 of this review for additional details. Overall there were no clinically meaningful changes in ECG parameters across the treatment groups.

There were 3 patients with chronic idiopathic constipation who had shifts to clinically significant ECGs (as assessed by the investigators) at the end of the treatment period. Two of the patients treated with Linaclotide 145µg in trial MCP-103-303 had normal ECGs at baseline (patients #0283003 and #0663003) which were abnormal and clinically significant at the end of treatment. One patient (#0880132) had an abnormal nonclinically significant ECG at baseline that became clinically significant by the end of the treatment period. All patients with chronic idiopathic constipation with postbaseline clinically significant ECG abnormalities are presented in the table below.

Table 80 List of Chronic idiopathic constipation Patients with Postbaseline Clinically Significant ECG abnormalities (as assessed by the Investigator) during the Treatment Period of the Phase 3 Double-Blind Placebo-Controlled Trials (Group 1) Safety Population

Treatment Group	Study Number	Patient ID/DPN	Age/Sex/Race	Date of First/Last Dose of Double - Blind Study Drug	Baseline Date	Baseline Result	Final/Last Assessment Date	Final/Last ECG Result	Comments
Placebo	LIN-MD-01	0100102	66/F/White	(b) (6)	2008-11-12	Abnormal, NCS	2009-03-16	Abnormal, NCS	
		0880132	37/F/Black or African American		2009-02-05	Abnormal, NCS	2009-05-27	Abnormal, CS	First degree AV block.
	MCP-103-303	0223006	85/M/White		2009-01-08	Abnormal, NCS	2009-04-17	Abnormal, NCS	
		0963003	68/M/White		2009-03-12	Abnormal, NCS	2009-05-18	Normal	
Linaclotide 145 ug	MCP-103-303	0283003	78/M/White		2009-02-11	Normal	2009-03-13	Abnormal, CS	atrial fibrillation
			0663003	60/F/White		2009-01-05	Normal	2009-04-13	Abnormal, CS

Source: Table 9.6.1 Applicants Integrated Summary of Safety pates 13055 – 13056.

Additional details on the patients with ECG findings reported as SAEs (patients #0283003 and #0663003 from Trial MCP-103-303) are provided in the SAE tables in Section 5.3.3. Patient #0880132 was treated with placebo during Trial LIN-MD-01. At the end of treatment, the investigator reported a TEAE of a clinically significant ECG finding (first-degree atrioventricular (AV) block). The first degree AV block was not noted at the Screening Visit (the PR interval was 204 msec at the Screening Visit and 208 msec at end of treatment).

There were 16 patients with chronic idiopathic constipation who had a post baseline potentially clinically significant value for at least 1 ECG parameter. Two patients treated with Linaclotide (vs. 3 patients with placebo) had prolonged QTc intervals over 500msec. Five patients had an increase in the QTc interval greater than 60msec. The incidence of post baseline potentially clinically significant ECG parameters are presented in the table below.

Table 81 Incidence of Post Baseline Potentially Clinically Significant ECG Parameters During Treatment Period of Chronic idiopathic constipation Patients in Phase 3 Double-Blind Placebo-Controlled Chronic idiopathic constipation Trials (Group 1) Safety Population

ECG Parameter (msec)	CC Patients		
	Placebo	Linaclotide	
	(N = 423)	145 ug (N = 430)	290 ug (N = 422)
	n/N1 (%)	n/N1 (%)	n/N1 (%)
QRS ≥ 150	4/415 (1.0)	2/413 (0.5)	0/405
PR ≥ 250	2/414 (0.5)	1/413 (0.2)	2/404 (0.5)
QTcB			
> 500	0/416	2/414 (0.5)	0/406
Change ≥ 60	1/416 (0.2)	0/414	1/406 (0.2)
QTcF			
> 500	1/416 (0.2)	0/414	0/406
Change ≥ 60	0/416	1/414 (0.2)	2/406 (0.5)

Source: Applicant's Table 10.2.1.3-1 Integrated Summary of Safety page 153.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies or clinical trials were submitted in support of this application.

7.4.6 Immunogenicity

The applicant did not perform immunogenicity testing during the clinical development. The applicant asserts that because Linaclotide is a small amino acid that is orally administered and minimally absorbed into the systemic circulation, any potential immunological response would likely be limited to the intestinal mucosa. The intestinal mucosal immune system acts primarily to suppress immune responses to the enormous quantities of antigens in ingested foods. Linaclotide is believed to be too small to be sufficiently antigenic to elicit humoral or cellular immunity without the addition of an adjuvant and/or carrier protein. An orally

administered peptide is not expected to produce as vigorous a response as that of a parenterally administered protein.

There are many complex factors that influence immunogenicity. The ability to evoke an immune response, and the nature and intensity of that response, depend not only on the physiochemical properties of the immunogen, but also on other factors including the characteristics of the organism being immunized, the route of contact, and the sensitivity of the methods used to detect the response.²³ The intestines contain the largest accumulation of lymphoid tissues in the body in the form of lymphoid aggregates in Peyer's patches and in the lamina propria (solitary lymphoid nodules) and as the scattered lymphocyte populations found in the epithelium and in the lamina propria.²⁴ The intestinal mucosa is under constant challenge by ingested foreign antigens in micro-organisms, products of food digestion and drugs.²⁴ Non-immune and immune mechanisms protect the lamina propria from immunogens. "Gastric acidity, digestive proteases in the gastrointestinal tract, intestinal mobility, the commensal microflora and the mucous coat or glyccolyx comprise some of the non-specific protective barriers."²⁴ Immune mechanisms may operate within the lumen of the gut, at the mucosal surface or within the lamina propria.

The stimulation of cells in the gut-associated lymphoid tissue (GALT) by intestinal antigens can result in either immunity or tolerance to that antigen and the factors that determine which effect predominates are not completely understood.²⁵ Proteins are, as a rule, the most effective immunogens.²³ Immunogenicity is influenced by molecular size and the most effective immunogens are proteins with molecular weights greater than 100,000 daltons.²³ Small molecules, such as amino acids, monoscaccharides, and most other species smaller than a molecular weight of 10, 000 daltons usually are not immunogenic.¹³ Homopolymers of a single amino acid may be poor immunogens, whereas copolymers of two or more amino acids may be induce a greater immunogenic response. Aromatic amino acids contribute more to immunogenicity than nonaromatic. There are a few substances below 1000 daltons that can induce immune responses but in most cases will do so only when bound to a larger, host-derived macro-molecule such as a protein.²³ "In the absence of the inflammatory stimuli necessary to elicit an immune response, oral administration of soluble protein antigens induces antigen-specific systemic non-responsiveness."²⁶

Linaclotide has a molecular weight of approximately 1569 daltons. Because Linaclotide is a new molecular entity and designed to treat a chronic condition, it is possible that the drug will elicit an antibody response. Given the limited systemic absorption of the drug and its mechanism of action, it is also possible that the manifestation of the immune response may mimic the pharmacology of the drug. In the opinion of this reviewer, it would have been preferable for the applicant to have performed an immunological assessment at least on a subset of patients. However, the applicant's rationale for not conducting immunogenicity is understandable.

7.5 Other Safety Explorations

Exploratory safety analyses for dose dependency, demographic interactions, drug-disease interactions and drug-drug interactions were consistent with the major safety results. Although there was some splitting of the TEAE preferred terms, the overall results did not change when the splitting was taken in to account. Diarrhea was the most common adverse event across all subanalyses. There were no distinguishable patterns in the types and incidence of TEAEs. Most adverse events occurred within the first month of study drug treatment (in most cases within the first week) and decreased over the 12 weeks of the treatment period. Patient demographics were similar across all treatment arms. The small proportion of patients over the age of 65 years may not reflect the larger U.S. population. Age, gender, and ethnicity did not appear to affect the incidence of TEAEs. There were no noteworthy differences in TEAEs, potentially clinically significant (PCS) vital signs and PCS ECG values across treatment groups. A higher proportion of Blacks relative to Caucasians had potentially clinically significant low-neutrophil counts. However, the differences did not appear to be related to study drug treatment. Almost a third of patients with chronic idiopathic constipation were obese (BMI $\geq 30\text{kg/m}^2$). The incidence of TEAEs in both obese and non-obese subgroups was comparable between the two Linaclotide doses. There were no notable differences in the occurrence of TEAEs or potentially clinically significant laboratory values between patients taking selective concomitant medications and those not taking concomitant medications. Because of the lack of systemic exposure following oral dosing, there were no clinical trials in special populations. Patients with pre-existing diabetes, hypertension, and other cardiovascular disorder had a safety profile that was consistent with the overall safety population of the double-blind placebo-controlled trials.

7.5.1 Dose Dependency for Adverse Events

There were two doses of Linaclotide (145 μg and 290 μg) administered during the double-blind placebo controlled Phase 3 trials in chronic idiopathic constipation patients. There were no distinguishable and consistent patterns in the types and incidence of treatment emergent adverse events experienced by patients taking the two doses. There were actually fewer patients in the Linaclotide 290 μg group (relative to Linaclotide 145 μg) who experienced common TEAEs. However, more patients in the 290 μg group experienced severe TEAEs.

7.5.2 Time Dependency for Adverse Events

For all treatment groups, there was a trend for adverse events to decrease over time. Most patients experienced adverse events within the first 4 weeks of treatment. The temporal occurrence of both gastrointestinal (GI) and non-GI TEAEs decreased over time. Such a pattern may indicate that individual patients are better able to tolerate study drug over time or it may reflect patient discontinuation from the trial but it is not possible to discern in this context. The time to occurrence of non-gastrointestinal TEAEs was similar among the treatment groups.

In the opinion of this reviewer, it would have been preferable for the applicant to have submitted data using smaller time intervals or at the very least time intervals that were of equal duration. For example, the applicant could have presented the data in weekly or monthly intervals as opposed to having 4 weeks in the first interval and 8 weeks in the second interval. Because of the mechanism of action for the proposed product, particular attention was given to the diarrhea TEAE. Among Linaclotide-treated patients, the incidence of diarrhea decreased from 12.0% in the first 4 weeks to 4.1% between weeks 4 to 12 and <1% after 12 weeks of treatment. Again such a pattern may represent improved patient tolerability, patient discontinuation, or decreased efficacy of the study drug product over time. Examining the time to onset of diarrhea alone does not allow the reviewer to determine causality. A presentation of the incidence of TEAEs for CIC patients by time to onset in the Phase 3 Double Blind Placebo-Controlled trials is provided in the table below.

Table 82 Treatment Emergent Adverse Events By Time to Onset Reported in At Least 2% of Linaclotide CIC Patients in Either Treatment Group of the Phase 3 Double-Blind Placebo-Controlled Trials (Group 1) and at an Incidence Greater than Placebo Safety Population

Adverse Event (Preferred Term)	Number (%) of Patients											
	Placebo			Linaclotide								
				145 µg/day			290 µg/day			Linaclotide Total		
	n (%)			n (%)			n (%)			n (%)		
	≤ 4 wks N = 423	4-12 wks [±] N = 401	> 12 wks N = 227	≤ 4 wks N = 430	4-12 wks [±] N = 403	>12 wks N = 224	≤ 4 wks N = 422	4-12 wks [±] N = 396	> 12 wks N = 213	≤ 4 wks N = 852	4-12 wks [±] N = 799	> 12 wks N = 437
Any TEAE	145	132 (32.9)	23 (10.1)	186 (43.3)	140 (34.7)	14 (6.3)	160 (37.9)	136 (34.3)	18 (8.5)	346 (40.6)	276 (34.5)	32 (7.3)
Diarrhea	12 (2.8)	6 (1.5)	2 (0.9)	56 (13.0)	17 (4.2)	1 (0.4)	46 (10.9)	16 (4.0)	0	102 (12.0)	33 (4.1)	1 (0.2)
Flatulence	18 (4.3)	3 (0.7)	1 (0.4)	22 (5.1)	3 (0.7)	0	16 (3.8)	5 (1.3)	0	38 (4.5)	8 (1.0)	0
Abdominal pain	7 (1.7)	6 (1.5)	0	8 (1.9)	9 (2.2)	0	13 (3.1)	8 (2.0)	0	21 (2.5)	17 (2.1)	0
Upper respiratory tract infection	10 (2.4)	7 (1.7)	0	11 (2.6)	12 (3.0)	0	8 (1.9)	6 (1.5)	0	19 (2.2)	18 (2.3)	0
Nausea	11 (2.6)	4 (1.0)	0	9 (2.1)	6 (1.5)	0	13 (3.1)	5 (1.3)	0	22 (2.6)	11 (1.4)	0
Abdominal distension	7 (1.7)	2 (0.5)	2 (0.9)	11 (2.6)	4 (1.0)	0	11 (2.6)	5 (1.3)	1 (0.5)	22 (2.6)	9 (1.1)	1 (0.2)
Nasopharyngitis	9 (2.1)	4 (1.0)	0	5 (1.2)	4 (1.0)	0	10 (2.4)	8 (2.0)	0	15 (1.8)	12 (1.5)	0
Sinusitis	4 (0.9)	4 (1.0)	0	4 (0.9)	8 (2.0)	2 (0.9)	2 (0.5)	8 (2.0)	1 (0.5)	6 (0.7)	16 (2.0)	3 (0.7)
Abdominal pain upper	4 (0.9)	1 (0.2)	2 (0.9)	6 (1.4)	7 (1.7)	0	5 (1.2)	0	0	11 (1.3)	7 (0.9)	0
Vomiting	7 (1.7)	2 (0.5)	0	5 (1.2)	0	0	5 (1.2)	5 (1.3)	0	10 (1.2)	5 (0.6)	0

Source: Table 8.1.1.1.2-1 Applicant's Submission Integrated Summary of Safety page 70.

TEAEs are ordered by decreasing frequency across the 3 time periods among all Linaclotide Total patients

TEAE = treatment-emergent adverse event; wks = weeks.

± 4-12 wks is defined as >4 weeks and ≤ 12 weeks.

7.5.3 Drug-Demographic Interactions

Patient demographics in the chronic idiopathic constipation Phase 3 Double-Blind Placebo Controlled trials were similar across all treatment arms. Most patients enrolled were Caucasian (76%), female (89%), and non-Hispanic (89%). The mean age across treatment arms was approximately 48 years. Approximately 12% (12.2%) were considered elderly (over the age of 65 years) by regulatory standards. Twenty-eight percent (28%) of all patients with chronic idiopathic constipation were obese (BMI ≥ 30 kg/m²). Approximately 20% (19.7%) also had hypertension. Approximately 5% also had diabetes and approximately 3% (2.6%) had cardiovascular disease.

Overall the proportion of patients over the age of 65 years who experienced TEAEs than relative those under age 65 years for all treatment groups were 65.5%, placebo, 64.7% 145 μ g Linaclotide, 57.1% Linaclotide 290 μ g respectively compared to 50.5% placebo, 60.4% Linaclotide 145 μ g, and 55.5% Linaclotide 290 μ g. The small proportion of patients enrolled in the trials who were over the age of 65 years may not be a complete reflection of the more generalized U.S. population. Clinical trials of Linaclotide may not include sufficient numbers of study participants over aged 65 years to determine whether they respond differently from younger individuals. However, with the exception of diarrhea and flatulence, there were minimal differences in the incidences of TEAEs based on age or treatment group. The incidence of diarrhea following Linaclotide treatment was higher in the ≥ 65 years group relative to the under 65 years old group (21.0% vs. 14.4% respectively. Placebo-treated patients who were ≥ 65 years also had a higher incidence of diarrhea than their younger counterparts (7.3% vs. 4.3%). Linaclotide patients over the age of 65 years experienced more flatulence (11.0%) than their counterparts the in placebo-treated patients (3.6%). However there were minimal differences in the incidence of flatulence among patients in the younger age group (4.5% Linaclotide vs. 5.4% placebo). There were no age-related noteworthy differences in the potentially significant laboratory, vital signs, and ECG values of Linaclotide-treated and placebo treated-patients.

There were minimal treatment-related differences based on sex in the incidence of specific TEAEs in chronic idiopathic constipation patients. The mean age of female patients with chronic idiopathic constipation was lower than that for males (47 years vs. 55 years) across treatment groups. This was reflective of the greater percentage of males patients with chronic idiopathic constipation who were \geq age 65 years. Overall, the incidence of TEAEs was lower in males than females (46.9% vs. 59.8%). Males in the 290 μ g Linaclotide group had a higher incidence of diarrhea, flatulence, and nausea relative to males in the Linaclotide 145 μ g and placebo groups. This effect was not observed in females. There no noteworthy gender-based differences in potentially clinically significant laboratory values, vital signs, and ECGs.

Table 83 Incidence of TEAEs in ≥ 2% and >2 Male or Female Chronic idiopathic constipation Patients During the Phase 3 Double-Blind Placebo-Controlled Phase 3 Clinical Trials (Group 1)

	Female				Male			
	Placebo (N =377)	Linaclotide			Placebo (N =46)	Linaclotide		
		145 ug (N = 386)	290 ug (N = 370)	Total (N =756)		145 ug (N = 44)	290 ug (N = 52)	Total (N = 96)
		n (%)	n (%)	n (%)		n (%)	n (%)	n (%)
Patients with at least one TEAE	204 (54.1)	242 (62.7)	210 (56.8)	452 (59.8)	18 (39.1)	20 (45.5)	25 (48.1)	45 (46.9)
Diarrhea	17 (4.5)	63 (16.3)	51 (13.8)	114 (15.1)	3 (6.5)	6 (13.6)	9 (17.3)	15 (15.6)
Flatulence	20 (5.3)	24 (6.2)	15 (4.1)	39 (5.2)	2 (4.3)	0	6 (11.5)	6 (6.3)
Abdominal pain	12 (3.2)	15 (3.9)	18 (4.9)	33 (4.4)	1 (2.2)	2 (4.5)	2 (3.8)	4 (4.2)
Upper respiratory tract infection	16 (4.2)	21 (5.4)	11 (3.0)	32 (4.2)	1 (2.2)	1 (2.3)	2 (3.8)	3 (3.1)
Nausea	14 (3.7)	14 (3.6)	14 (3.8)	28 (3.7)	1 (2.2)	1 (2.3)	4 (7.7)	5 (5.2)
Headache	18 (4.8)	15 (3.9)	17 (4.6)	32 (4.2)	1 (2.2)	0	0	0
Abdominal distension	8 (2.1)	15 (3.9)	13 (3.5)	28 (3.7)	2 (4.3)	0	2 (3.8)	2 (2.1)
Urinary tract infection	15 (4.0)	15 (3.9)	12 (3.2)	27 (3.6)	0	0	0	0
Nasopharyngitis	13 (3.4)	7 (1.8)	16 (4.3)	23 (3.0)	0	2 (4.5)	1 (1.9)	3 (3.1)
Sinusitis	8 (2.1)	13 (3.4)	11 (3.0)	24 (3.2)	0	0	0	0
Abdominal pain upper	7 (1.9)	13 (3.4)	4 (1.1)	17 (2.2)	0	0	1 (1.9)	1 (1.0)
Back pain	10 (2.7)	7 (1.8)	6 (1.6)	13 (1.7)	0	0	2 (3.8)	2 (2.1)
Dizziness	2 (0.5)	3 (0.8)	5 (1.4)	8 (1.1)	0	1 (2.3)	1 (1.9)	2 (2.1)
Skin laceration	0	1 (0.3)	1 (0.3)	2 (0.3)	0	0	3 (5.8)	3 (3.1)
Abdominal pain lower	5 (1.3)	0	1 (0.3)	1 (0.1)	0	1 (2.3)	1 (1.9)	2 (2.1)
Rectal hemorrhage	2 (0.5)	1 (0.3)	0	1 (0.1)	1 (2.2)	0	2 (3.8)	2 (2.1)

Source: Applicant's Table 11.1.2.1-1 Integrated Summary of Safety page 161.

Race did not appear to be a major factor in the incidence of TEAEs. Black patients experienced GI TEAEs less frequently than their White counterparts. The incidence of diarrhea was 5.5% in placebo-treated Caucasians and 17.1% in Linaclotide-treated Caucasians. The incidence of diarrhea was 2.3% in Blacks treated with placebo and 7.6% in Linaclotide-treated Blacks. Across the two Linaclotide doses, there were minimal differences between the TEAEs experienced by Blacks and Whites.

Higher percentages of Black patients had potentially clinically significant low neutrophil counts, but the differences between Caucasian and Black patients did not appear to be related to treatment. In the Black patients with chronic idiopathic constipation, 2.2% of the Linaclotide-treated group and 8.5% of the placebo-treated group had potentially clinically significant low neutrophils compared with 1.6% and 0.3% for the Linaclotide-treated and placebo groups of Caucasian patients with chronic idiopathic constipation. "The definition of neutropenia is categorically based and represents a range that is arbitrarily considered subnormal. It is typically defined by an absolute neutrophil count (ANC) less than 1.5×10^9 cells/L."²⁷ Benign ethnic neutropenia (BEN) has been used to describe a condition in individuals of African descent with neutrophil counts less than 1.5×10^9 cells/L in the absence

of other causes.²⁷ The etiology of benign ethnic neutropenia is not well understood. However benign ethnic neutropenia is not associated with an increase risk of infections and there are no compensatory increases in lymphocytes or monocytes.²⁷ Outside of the United States, BEN has been described in up to 25% to 40% of those of African descent.¹⁷ In the United States, the prevalence decreases with age and is much lower: 4% in adult African American men and 2% to 3% in adult African American women, compared with less than 1% in whites.¹⁷ BEN is typically diagnosed by repeated ANC values less than 1.5×10^9 cells/L over many months, in the absence of other secondary neutropenia. Recent population-based analysis showed that most BEN-related neutrophil measurements are at least 1.0×10^9 cells/L.¹⁷ This is somewhat reassuring and lends credence to the argument that the differences between Caucasians and Blacks did not appear to be treatment-related.

There were no apparent differences in TEAEs between Linaclotide-treated and placebo-treated patients based on ethnicity. Diarrhea was the only TEAE for which there was a clear relationship to Linaclotide treatment regardless of ethnic classification. The incidence of diarrhea in Linaclotide-treated Hispanic patients [11.0% (vs. 2.8% in placebo-treated Hispanic patients)] was slightly lower than the incidence in non-Hispanic patients who were treated with Linaclotide [15.6% (vs. 4.9% in placebo-treated Non-Hispanic patients)]. The TEAE rates for GI events were similar across both doses of Linaclotide in non-Hispanic patients. The incidence of GI TEAEs was higher with the 290 μ g dose than with the 145 μ g dose in Hispanic patients. Ethnicity did not affect the potentially clinically significant laboratory values, vital signs, and ECG values.

Almost a third (30.2%) of patients with chronic idiopathic constipation in the double-blind placebo controlled trials were obese (BMI ≥ 30 kg/m²). Obesity was more prevalent among Blacks (34%) than Whites (16%). Consistent with the other demographic characteristics, the incidence of diarrhea in obese patients treated with Linaclotide was higher than placebo (15.4% vs. 2.1%). The incidence of diarrhea was similar between the obese and non-obese patients treated with Linaclotide (15.4% vs. 15.1%). The incidence of diarrhea was slightly higher in the non-obese placebo-treated patients (6.4%) relative to the obese placebo-treated patients (2.1%). The incidence of TEAEs in both obese and non-obese subgroups was comparable between the two Linaclotide doses. More obese patients taking Linaclotide 145 μ g experienced at least one TEAE than any other treatment groups (66.4%). Obese patients taking Linaclotide 145 μ g (20.8%) experienced more diarrhea than those taking the 290 μ g dose (9.5%). This was not seen in non-obese patients. The following table provides a comparison of the incidence of TEAEs in $\geq 2\%$ and ≥ 2 Obese or non-Obese CC Patients in the pivotal Phase 3 trials (Group 1).

Table 84 Incidence of Treatment-Emergent Adverse Events in $\geq 2\%$ and ≥ 2 Obese or Non-Obese Chronic idiopathic constipation Patients Receiving Linaclotide during the Phase 3 Double-Blind Placebo-Controlled Trials (Group 1) Safety Population

	< 30 kg/m ²				≥ 30 kg/m ²			
		Linaclotide				Linaclotide		
	Placebo (N =279)	145 ug (N = 305)	290 ug (N = 306)	Total (N =611)	Placebo (N =144)	145 ug (N = 125)	290 ug (N = 116)	Total (N =241)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with at least one TEAE	145 (52.0)	179 (58.7)	172 (56.2)	351 (57.4)	77 (53.5)	83 (66.4)	63 (54.3)	146 (60.6)
Diarrhea	17 (6.1)	43 (14.1)	49 (16.0)	92 (15.1)	3 (2.1)	26 (20.8)	11 (9.5)	37 (15.4)
Flatulence	15 (5.4)	17 (5.6)	17 (5.6)	34 (5.6)	7 (4.9)	7 (5.6)	4 (3.4)	11 (4.6)
Abdominal pain	9 (3.2)	12 (3.9)	16 (5.2)	28 (4.6)	4 (2.8)	5 (4.0)	4 (3.4)	9 (3.7)
Upper respiratory tract infection	10 (3.6)	12 (3.9)	10 (3.3)	22 (3.6)	7 (4.9)	10 (8.0)	3 (2.6)	13 (5.4)
Nausea	12 (4.3)	13 (4.3)	15 (4.9)	28 (4.6)	3 (2.1)	2 (1.6)	3 (2.6)	5 (2.1)
Headache	14 (5.0)	12 (3.9)	17 (5.6)	29 (4.7)	5 (3.5)	3 (2.4)	0	3 (1.2)
Abdominal distension	8 (2.9)	11 (3.6)	9 (2.9)	20 (3.3)	2 (1.4)	4 (3.2)	6 (5.2)	10 (4.1)
Urinary tract infection	9 (3.2)	11 (3.6)	10 (3.3)	21 (3.4)	6 (4.2)	4 (3.2)	2 (1.7)	6 (2.5)
Nasopharyngitis	6 (2.2)	5 (1.6)	11 (3.6)	16 (2.6)	7 (4.9)	4 (3.2)	6 (5.2)	10 (4.1)
Sinusitis	8 (2.9)	12 (3.9)	8 (2.6)	20 (3.3)	0	1 (0.8)	3 (2.6)	4 (1.7)
Abdominal pain upper	5 (1.8)	9 (3.0)	3 (1.0)	12 (2.0)	2 (1.4)	4 (3.2)	2 (1.7)	6 (2.5)
Back pain	4 (1.4)	5 (1.6)	7 (2.3)	12 (2.0)	6 (4.2)	2 (1.6)	1 (0.9)	3 (1.2)
Vomiting	6 (2.2)	4 (1.3)	8 (2.6)	12 (2.0)	3 (2.1)	1 (0.8)	2 (1.7)	3 (1.2)
Bronchitis	4 (1.4)	2 (0.7)	2 (0.7)	4 (0.7)	5 (3.5)	3 (2.4)	3 (2.6)	6 (2.5)
Arthralgia	2 (0.7)	0	3 (1.0)	3 (0.5)	3 (2.1)	2 (1.6)	3 (2.6)	5 (2.1)
Oropharyngeal pain	3 (1.1)	1 (0.3)	2 (0.7)	3 (0.5)	3 (2.1)	5 (4.0)	0	5 (2.1)

Source: Table 11.1.5.1.1-1 Applicant's Integrated Summary of Safety page 170.

7.5.4 Drug-Disease Interactions

Because of the lack of systemic exposure following oral dosing, there were no clinical studies in special populations (e.g. patients with hepatic impairment or renal impairment). The metabolism of Linaclotide occurs by proteolysis in the GI tract and therefore changes in liver function would not be expected to alter Linaclotide clearance. The risk of altered clearance in renally or hepatically impaired patients is presumed to be minimal.

The applicant chose to perform special evaluations of patients with certain comorbid medical conditions at baseline, making them potentially susceptible to the consequences of fluid shifts and electrolyte changes as a result of severe diarrhea. Hypertension, diabetes, and cardiovascular disorders were appropriately chosen for analysis because of their wide prevalence in the general population. Diabetes is estimated to affect 25.8 million people of all ages (approximately 8.3% of the U.S. population.)²⁸ Another 76.4 million adults in the United States have been diagnosed with high blood pressure (approximately 30%).²⁹ In 2008, heart disease caused almost 25% of deaths in the United States.³⁰

Across all treatment groups, (placebo, Linaclotide 145µg and Linaclotide 290µg), over 50% of the patients with hypertension and diabetes mellitus at baseline experienced at least one TEAE. A higher proportion of patients on placebo with comorbid cardiovascular disorders (60%) experienced at least one TEAE relative to both the Linaclotide 145µg and Linaclotide 290µg arms (33.3% and 30.8% respectively). However, these percentages may be somewhat exaggerated given the small denominators (i.e. small number of patients with diabetes and cardiovascular disorders at baseline.)

Of the patients with chronic idiopathic constipation enrolled in the double-blind, placebo controlled trials, there were 260 patients who had hypertension at baseline (92 on placebo, 90 on Linaclotide 145µg, and 78 on Linaclotide 290µg). There did not appear to be any appreciable differences in the incidence of treatment emergent adverse events between hypertensive patients treated with Linaclotide and the overall safety population treated with Linaclotide. Analysis of the TEAEs did not reveal any evidence to suggest that any of the adverse consequences of fluid or electrolyte shifts that may result from Linaclotide adversely impacted patients with hypertension. With the exception of the GI SOC, overall patients with hypertension on Linaclotide did not experience more TEAEs than those hypertensive patients who were taking placebo. A slightly higher proportion of patients in the Linaclotide arms experienced more TEAEs from the Vascular Disorders SOC relative to placebo (0% placebo, 1.1% Linaclotide 145µg, 5.1% Linaclotide 290µg respectively). However, the crude numbers were small (1 patient treated with Linaclotide 145µg and 4 patients treated with Linaclotide 290µg). In many cases, hypertensive patients in the placebo arm experienced more TEAEs than those in the Linaclotide arms. It is worth mentioning that of the Linaclotide-treated patients with chronic constipation, the laboratory parameters that were potentially clinically significant at an incidence of $\geq 2\%$ were low lymphocyte count (3.1% vs. 2.2% for placebo), high glucose (3.1% vs. 2.2% for placebo), low potassium (2.5% vs. 2.3% for placebo), and decreased weight (2.4% vs. 1.1% for placebo). Low white blood cell counts were also noted

to occur during the analysis of the safety population for each of the double-blind placebo-controlled trials.

Given that almost a third of patients with chronic idiopathic constipation in the Linaclotide trials were obese, it was somewhat surprising to find that only 67 of these patients had pre-existing diabetes. Consistent with previous subgroup analyses, the incidence of diarrhea was higher in diabetics treated with Linaclotide relative to placebo (36.1% in the Linaclotide 145µg arm, 26.1% in the Linaclotide 290µg arm, and 18.2% in the placebo arm respectively). A slightly higher proportion of diabetic patients in the Linaclotide 145µg arm also experienced more TEAEs from the Infections and Infestations SOC. However, overall there did not appear to be any substantive differences in safety parameters between Linaclotide-treated diabetics and the overall safety population treated with Linaclotide.

Like the diabetic subpopulation, there was a very small number of patients with chronic idiopathic constipation with other cardiovascular disorders at baseline (n=37). The small number may inadequately represent the greater U.S. population and therefore the results of the TEAEs analysis for this subpopulation should be cautiously interpreted. There was no evidence to suggest that patients with cardiovascular disorders who were treated with Linaclotide experienced more TEAEs secondary to fluid and electrolyte shifts relative to the overall safety population.

The number of patients with chronic idiopathic constipation with each of the pre-existing comorbidities who experienced at least one TEAE is presented in the table below. The SOC and preferred term of selected commonly occurring TEAEs is also presented.

Table 85 Incidence of TEAEs in Chronic idiopathic constipation Patients with Pre-Existing Diseases by Selected SOC and Selected Preferred Terms Phase 3 Double-Blind Placebo Controlled Trials (Group 1) Safety Population

Co-morbid Disease History (SOC) (Preferred Term)	Placebo n/N (%)	Linaclotide		
		145 µg/day n/N (%)	290 µg/day n/N (%)	Linaclotide Total n/N (%)
Patients who experienced at least one TEAE				
Hypertension	53/92 (57.6%)	57/90 (63.3%)	41/78 (52.6%)	98/168 (58.3%)
<i>Cardiac Disorders</i>	4/92 (4.3%)	2/90 (2.2%)	0/78	2/168 (1.2%)
First Degree AV Block	1/92 (1.1%)	0	0	0
Palpitations	1/92 (1.1%)	0	0	0
Atrial Fibrillations	2/92 (2.2%)	0	0	0
Sinus Tachycardia	0	1/90 (1.1%)	0	1/168 (0.6%)
Ventricular Extrasystoles	0	1/90 (1.1%)	0	1/168 (0.6%)
<i>Gastrointestinal Disorders</i>	18/92 (19.6%)	27/90 (30.0%)	20/78 (25.6%)	47/168 (28.0%)
Diarrhea	6/92 (6.5%)	19/90 (21.1%)	8/78 (10.3%)	27/168 (16.1%)
Flatulence	3/92 (3.3%)	1/90 (1.1%)	3/78 (3.8%)	4/168 (2.4%)
Abdominal distension	1/92 (1.1%)	2/90 (2.2%)	4/78 (5.1%)	6/168 (3.6%)
Abdominal pain	2/92 (2.2%)	2/90 (2.2%)	3/78 (3.8%)	5/168 (3.0%)
Fecal incontinence	1/92 (2.2%)	1/90 (1.1%)	1/78 (1.3%)	2/168 (1.2%)
<i>General disorders & administration site conditions</i>	5/91 (5.4%)	2/90 (2.2%)	4/78 (5.1%)	6/168 (3.6%)
Peripheral edema	1/92 (1.1%)	2/90 (2.2%)	0/78	2/168 (1.2%)
Chest pain	0	0	1/78 (1.3%)	1/168 (0.6%)
<i>Infections and infestations</i>	18/92 (19.6%)	19/90 (21.1%)	13/78 (16.7%)	32/168 (19.0%)
<i>Investigations</i>	5/92 (5.4%)	6/90 (6.7%)	5/78 (6.4%)	11 (6.5%)
Blood Pressure increase	0	0	0	0
Blood Pressure decrease	0	0	0	0
Blood Magnesium decreased	0	0	1/78 (1.3%)	1/168 (0.6%)
Blood Potassium increased	0	0	0	0
Blood Potassium decreased	0	0	1/78 (1.3%)	1/168 (0.6%)
Blood Bicarbonate decreased	0	0	0	0
Blood Sodium increase	0	0	0	0
Blood Sodium decrease	0	0	0	0
Weight decreased	0	0	0	0
Weight increased	0	0	0	0
<i>Metabolism and Nutrition</i>	6/93 (6.5%)	3/90 (3.3%)	3/78 (3.8%)	6/168 (3.6%)
<i>Renal and Urinary Disorders</i>	3/92 (3.3%)	3/90 (3.3%)	2/78 (2.6%)	5/168 (3.0%)
Hematuria	1/92 (1.1%)	2/90 (2.2%)	0	2/168 (1.2%)
Azotemia	0	0	1/78 (1.3%)	1/168 (0.6%)
Proteinuria	1/92 (1.1%)	0	0	0
<i>Respiratory, thoracic and mediastinal disorders</i>	6/92 (6.5%)	5/90 (5.6%)	2/78 (2.6%)	7/168 (4.2%)
<i>Skin and subcutaneous tissue disorders</i>	3/92 (3.3%)	2/90 (2.2%)	5/78 (6.4%)	7/168 (4.2%)
<i>Vascular disorders</i>	0	1 (1.1%)	4 (5.1%)	5/168 (3.0%)
Hypertension	0	1 (1.1%)	3 (3.8%)	4/168 (2.4%)
Orthostatic hypotension	0	0	1 (1.3%)	1/168 (0.6%)

Co-morbid Disease History (SOC) (Preferred Term)	Placebo n/N (%)	Linaclotide		
		145 µg/day n/N (%)	290 µg/day n/N (%)	Linaclotide Total n/N (%)
Patients who experienced at least one TEAE				
Diabetes Mellitus	12/22 (54.5%)	15/22 (68.2%)	12/23 (52.2%)	23/45 (60.0%)
Cardiac Disorders	2/22 (9.1%)	0	0	0
First Degree AV Block	0	0	0	0
Palpitations	0	0	0	0
Atrial Fibrillations	1/22 (4.5%)	0	0	0
Sinus Tachycardia	0	0	0	0
Ventricular Extrasystoles	0	0	0	0
Gastrointestinal Disorders	4/22 (18.2%)	7/22 (31.8%)	6/23 (26.1%)	13/45 (28.9%)
Diarrhea	0	6/22 (27.3%)	2/23 (8.7%)	8/45 (17.8%)
Flatulence	3/22 (13.6%)	1/22 (4.5%)	2/23 (8.7%)	3/45 (6.7%)
Abdominal distension	0	1/22 (4.5%)	3/23 (13.0%)	4/45 (8.9%)
Abdominal pain	0	0	1/23 (4.3%)	1/45 (2.2%)
Fecal incontinence	0	1 (4.5%)	0	1/45 (2.2%)
General disorders & administration site conditions	2/22 (9.1%)	0	0	0
Peripheral edema	0	0	0	0
Chest pain	0	0	0	0
Infections and infestations	5/22 (22.7%)	6/22 (27.3%)	3/23 (13.0%)	9/20 (20.0%)
Investigations	3/22 (13.6%)	1/22 (4.5%)	4/23 (17.4%)	5/45 (11.1%)
Blood Pressure increase	0	0	0	0
Blood Pressure decrease	0	0	0	0
Blood Magnesium decreased	0	0	1/23 (4.3%)	1/45 (2.2%)
Blood Potassium increased	0	0	0	0
Blood Potassium decreased	0	0	0	0
Blood Bicarbonate decreased	0	0	0	0
Blood Sodium increase	0	0	0	0
Blood Sodium decrease	0	0	0	0
Weight decreased	0	0	0	0
Weight increased	0	0	0	0
Metabolism and Nutrition	3/22 (13.6%)	2/22 (9.1%)	1/23 (4.3%)	3/45 (6.7%)
Renal and Urinary Disorders	0	1/22 (4.5%)	1/23 (4.3%)	2/45 (4.4%)
Hematuria	0	0	0	0
Azotemia	0	0	0	0
Proteinuria	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1/22 (4.5%)	1/22 (4.5%)	0	1/45 (2.2%)
Skin and subcutaneous tissue disorders	2/22 (9.1%)	0	2/23 (8.7%)	2/45 (4.4%)
Vascular disorders	0	0	1/23 (4.3%)	1/45 (2.2%)
Hypertension	0	0	1/23 (4.3%)	1/45 (2.2%)
Orthostatic Hypotension	0	0	0	0

Co-morbid Disease History (SOC) (Preferred Term)	Placebo n/N (%)	Linaclotide		
		145 µg/day n/N (%)	290 µg/day n/N (%)	Linaclotide Total n/N (%)
Patients who experienced at least one TEAE				
Other Cardiovascular Disorders	6/15 (60.0%)	3/9 (33.3%)	4/13 (30.8%)	7/22 (31.8%)
<i>Cardiac Disorders</i>	1/15 (6.7%)	0	0	0
First Degree AV Block	0	0	0	0
Palpitations	0	0	0	0
Atrial Fibrillations	1/15 (6.7%)	0	0	0
Sinus Tachycardia	0	0	0	0
Ventricular Extrasystoles	0	0	0	0
<i>Gastrointestinal Disorders</i>	6/15 (40.0%)	1/9 (11.1%)	3/13 (23.1%)	4/22 (18.2%)
Diarrhea	2/15 (13.3%)	0	1/13 (7.7%)	1/22 (4.5%)
Flatulence	2/15 (13.3%)	0	1/13 (7.7%)	1/22 (4.5%)
Abdominal distension	1/15 (6.7%)	1/9 (11.1%)	1/13 (7.7%)	2/22 (9.1%)
Abdominal pain	0	0	0	0
Fecal incontinence	1/15 (6.7%)	0	0	0
<i>General disorders & administration site conditions</i>	1/15 (6.7%)	0	0	0
Peripheral edema	0	0	0	0
Chest pain	0	0	0	0
<i>Infections and infestations</i>	3/15 (20.0%)	2/9 (22.2%)	1/13 (7.7%)	3/22 (13.6%)
<i>Investigations</i>	0	0	0	0
Blood Pressure increase	0	0	0	0
Blood Pressure decrease	0	0	0	0
Blood Magnesium decreased	0	0	0	0
Blood Potassium increased	0	0	0	0
Blood Potassium decreased	0	0	0	0
Blood Bicarbonate decreased	0	0	0	0
Blood Sodium increase	0	0	0	0
Blood Sodium decrease	0	0	0	0
Weight decreased	0	0	0	0
Weight increased	0	0	0	0
<i>Metabolism and Nutrition</i>	2/15 (13.3%)	0	1/13 (7.7%)	1/22 (4.5%)
Fluid Retention	0	0	1/13 (7.7%)	1/22 (4.5%)
<i>Renal and Urinary Disorders</i>	1/15 (6.7%)	0	0	0
Hematuria	0	0	0	0
Azotemia	0	0	0	0
Proteinuria	0	0	0	0
<i>Respiratory, thoracic and mediastinal disorders</i>	0	1/9 (11.1%)	0	1/22 (4.5%)
<i>Skin and subcutaneous tissue disorders</i>	2/15 (13.3%)	0	0	0
<i>Vascular disorders</i>	0	0	0	0

Source: Reviewers Table Adapted from Applicants After-text Tables 10.1.1A, 10.1.1B, 10.1.1C, Integrated Summary of Safety pages 13057 - 13089

TEAE = Treatment Emergent Adverse Events

n=number of patients in the treatment group that experienced at least one TEAE

N = Number of patients in the treatment group with the Disease at Baseline.

The incidence of on-therapy SAEs in patients with chronic idiopathic constipation with each of the prespecified co-morbid conditions are presented in the table below. Interestingly, patients on placebo in each of the subpopulations experienced more SAEs relative to both of the Linaclotide treatment arms.

Table 86 Incidence of On-Therapy Serious Adverse Events (SAEs) in patients with Pre-Existing Diseases at Baseline by SOC and Preferred Term -- Phase 3 Double-Blind Placebo-Controlled Trials (Group 1) Safety Population

Patients with Pre-Existing Disease who experienced at least one SAE	Placebo	Linaclotide		
		145 µg/day	290 µg/day	Linaclotide Total
Hypertension n/N (%) Number of patients with SAEs/100 patient-years	7/92 (7.6%) 35.4	2/90 (2.2%) 10.2	4/78 (5.1%) 25.3	6/168 (3.6%) 16.9
Diabetes Mellitus n/N (%) Number of patients with SAEs/100 patient-years	3/22 (13.6%) 62.3	0/22 0	1/23 (4.3%) 19.4	1/45 (2.2%) 10.7
Other cardiovascular disorders n/N (%) Number of patients with SAEs/100 patient-years	2/15 (13.3%) 58.5	0/9 0	0/13 0	0/22 0

Source: Reviewer's Table Adapted from Table 10.1.2A, 10.1.2B, and 10.1.2C Applicants Integrated Summary of Safety pages 13090
 n=number of patients in the group that experienced at least one SAE
 N = Number of patients with the Disease at Baseline

Overall analyses of potentially clinically significant laboratory data, vital signs data, and ECG data did not reveal any noteworthy differences in any of the parameters between patients with hypertension, diabetes, or cardiovascular disorders relative to the larger safety population.

7.5.5 Drug-Drug Interactions

There were no clinical studies assessing drug-drug interactions.

In vitro studies show that Linaclotide is not a substrate, inhibitor, or inducer of cytochrome P450 enzymes. At clinically relevant concentrations, Linaclotide is not a substrate for P-glycoprotein and does not inhibit common efflux and uptake transporters. The minimal systemic exposure to Linaclotide and the active metabolite, MM419447 following oral administration of the drug; the extensive metabolism of both peptides within the lumen of the GI tract; and the lack of interaction with common drug-transporting and drug-metabolizing enzymes support the argument that Linaclotide is unlikely to interact with concomitantly administered medications.

According to the applicant, potential clinical interactions between Linaclotide and drug classes commonly used by patients with chronic idiopathic constipation were explored by comparing the treatment emergent adverse events profiles of patients taking Linaclotide with

the treatment emergent adverse events in patients taking placebo during the Phase 3 double-blind placebo controlled trials. (See section 7.2.6 for additional information.) The applicant chose to evaluate patients using diuretics; agents acting on the renin-angiotensin system; proton-pump inhibitors; laxatives and mineral supplements; psychoanaleptics including selective serotonin reuptake inhibitors and other antidepressants. These drugs were chosen because they are commonly used in patients with CIC and because of their potential to induce diarrhea, electrolyte changes, and volume depletion. The applicant may have also considered evaluating anti-cholinergics as these are commonly administered for pain and cramping in patients with IBS-C. However, for the CIC patient population, the choice of medications seems reasonable. The incidence of TEAEs in patients taking each of the aforementioned class of medications is presented in the table below.

Table 87 Incidence of TEAEs in Chronic idiopathic constipation Patients Taking Selected Concomitant Medications during Treatment Period Phase 3 Double-Blind Placebo Controlled Trials (Group 1) Safety Population.

Concomitant Medication	Placebo n/N (%)	Linaclotide		
		145 µg/day n/N (%)	290 µg/day n/N (%)	Linaclotide Total n/N (%)
Patients taking Concomitant Diuretics with at least one TEAE	19/40 (47.5%)	13/27 (48.1%)	20/29 (69%)	33/56 (58.9%)
Patients taking Concomitant Agents Acting on the Renin-Angiotensin System with at least one TEAE	33/56 (58.9%)	41/61 (67.2%)	26/53 (49.1%)	67/114 (58.8%)
Patients taking Concomitant Proton Pump Inhibitors with at least one TEAE	42/61 (68.9%)	41/57 (71.9%)	35/67 (52.2%)	76/124 (61.3%)
Patients taking Concomitant Laxatives and Mineral Supplements with at least one TEAE	23/36 (63.9%)	29/46 (63.0%)	17/29 (58.6%)	46/75 (61.3%)
Patients taking Concomitant Psychoanaleptics with at least one TEAE	2/6 (33.3%)	10/11 (90.9%)	7/12 (58.3%)	17/23 (73.9%)
Patients taking Concomitant Selective Serotonin Reuptake Inhibitors with at least one TEAE	34/63 (54.0%)	29/44 (65.9%)	24/36 (66.7%)	53/80 (66.3%)
Patients Taking Concomitant Antidepressants with at least one TEAE	22/39 (56.4%)	33/48 (68.8%)	19/30 (63.3%)	52/78 (66.7%)

Source: Reviewers Table Adapted from Applicants After-text Tables 10.2.1A, 10.2.1B, 10.2.1C, 10.2.1D, 10.2.1E, 10.2.1F, and 10.2.1G Integrated Summary of Safety pages 13132 – 13231

TEAE = Treatment Emergent Adverse Events

n=number of patients experiences TEAEs

N = Number of patients taking Class of Concomitant Medication

When one considers that there were 1275 patients in the combined Phase 3 Double-Blind Placebo-Controlled Trials, the proportion of patients taking concomitant medication in each of the treatment arm is relatively small. The most common concomitant medications were the PPIs, agents acting on the renin-angiotensin system, selective serotonin reuptake inhibitors (SSRIs), and other antidepressants. Again there was some splitting of preferred terms during the analysis of these TEAEs, especially for “abdominal pain.”

For both Linaclotide and placebo treatment arms, diarrhea occurred at a higher rate in patients with chronic idiopathic constipation taking concomitant proton pump inhibitors or laxatives compared to other patients in the Double-Blind Placebo controlled trials. It is not

completely clear why this same pattern was not seen in IBS-C patients since the etiology of constipation is thought to be very similar for IBS-C and chronic idiopathic constipation. There was also a high incidence of diarrhea TEAEs reported in patients taking concomitant SSRIs and psychoanaleptics. The incidence of diarrhea in patients taking each of the selected concomitant medications is presented in the table below.

Table 88 Incidence of Diarrhea in Chronic idiopathic constipation Patients Taking PPIs, Laxatives, Psychoanaleptics, SSRIs, Diuretics, and Agents Acting on the Renin-Angiotensin System During the Phase 3 Double-Blind Placebo Controlled Trials (Group1) Safety Population

Diarrhea	CC Patients			
	Placebo	Linaclotide		
		145 µg	290 µg	Total
Group 1 n/N ^a (%)	20/423 (4.7%)	69/430 (16.0%)	60/422 (14.2%)	129/852 (15.1%)
PPI n/N1 (%)	6/61 (9.8%)	16/57 (28.1%)	10/67 (14.9%)	26/124 (21.0%)
Laxative n/N1 (%)	3/36 (8.3%)	7/46 (15.2%)	7/29 (24.1%)	14/75 (18.7%)
Psychoanaleptics n/N1 (%)	0/6 (0%)	7/11 (20.8%)	4/12 (33.3%)	11/23 (47.8%)
SSRIs n/N1 (%)	1/63 (1.6%)	10/44 (22.7%)	6/36 (16.7%)	16/80 (20.0%)
Diuretics n/N1 (%)	3/40 (7.5%)	6/27 (22.2%)	1/29 (3.4%)	7/56 (25.0%)
Agents Acting on the Renin-Angiotensin System n/N1 (%)	5/56 (8.9%)	15/61 (24.6%)	4/53 (7.5%)	19/114 (16.7%)
Antidepressants n/N1 (%)	2/39 (5.1%)	10/48 (20.8%)	5/30 (16.7%)	15/78 (19.2%)

Source: Reviewers Table Adapted from Applicants After-text Tables 10.2.1A, 10.2.1B, 10.2.1C, 10.2.1D, 10.2.1E, 10.2.1F, 10.2.1G and Applicants Table 11.2.1-1 Integrated Summary of Safety page 174.

a. Safety Population

N = number of patients in Safety Population;

N1 = number of patients in population taking the indicated concomitant medication;

n = number of patients with diarrhea

In addition to diarrhea and the gastrointestinal TEAEs, the reviewer closely reviewed the incidence of electrolyte abnormalities, cardiac disorders, and other TEAEs that may be indicative of shifts in fluid status secondary to dehydration, hypovolemia, or hypervolemia. Attention was given to adverse reactions that also appeared in the currently approved labeling of the products in each drug class (e.g. hypomagnesemia associated with PPI therapy).

Overall for chronic idiopathic constipation, the proportion of patients who took concomitant diuretics with the Linaclotide 290µg and experienced a TEAE was higher (69%) than the proportion in the Linaclotide 145µg (48.1%) and placebo groups (47.5%). Interestingly, patients in the Linaclotide 290µg group did not experience more GI related TEAEs or diarrhea. This may be consistent with the argument that the 290µg Linaclotide dose does not offer any additional pharmacodynamic benefit. Otherwise, for those patients that were taking concomitant diuretics, there were no notable differences in the incidence of TEAEs across treatment groups. The reviewer chose to present the overall number of patients taking concomitant diuretics and experiencing TEAEs in the table below. Particular attention was given to the GI SOC, cardiac disorders SOC, vascular SOC, investigations SOC, metabolism and nutrition SOC, and renal and urinary disorders SOC. In patients taking diuretics or agents affecting the renin-angiotensin system, the incidence of potentially clinically significant changes in electrolytes was not meaningfully different between the Linaclotide groups and placebo. The incidence of selected TEAEs associated with concomitant use of PPIs, laxatives and mineral Supplement, and agents acting on the renin-angiotensin system are also presented in the following tables.

Table 89 Incidence of Selected TEAEs in Chronic idiopathic constipation Patients who took Concomitant Diuretics During 12-Week Treatment Period of Phase 3 Double-Blind, Placebo-Controlled Trials (Group 3) Safety Population

TEAE SOC (Preferred Term)	Placebo N=40	Linaclotide		
		145 µg/day N=27	290 µg/day N=29	Linaclotide Total N=56
	n (%)	n (%)	n (%)	n (%)
Patients with at least one TEAE	19 (47.5%)	13 (48.1%)	20 (69%)	33 (58.9%)
Cardiac disorders SOC	1 (2.5%)	0	0	0
Atrial fibrillation	1 (2.5%)			
Gastrointestinal Disorders SOC	7 (17.5%)	8 (29.6%)	6 (20.7%)	14 (25.0%)
Diarrhea	3 (7.5%)	6 (22.2%)	1 (3.4%)	7 (12.5%)
Flatulence	1 (2.5%)	1 (3.7%)	3 (10.3%)	4 (7.1%)
Abdominal distension	0	1 (3.7%)	2 (6.9%)	3 (5.4%)
Nausea	0	0	0	0
Abdominal tenderness	0	1 (3.7%)	0	1 (1.8%)
Abdominal pain	2 (5.0%)	0	0	0
Abdominal pain upper	0	0	0	0
Frequent bowel movements	0	0	0	0
Fecal incontinence	1 (2.5%)	2 (7.4%)	0	2 (3.6%)
Investigations SOC	1 (2.5%)	2 (7.4%)	4 (13.8%)	6 (10.7%)
Metabolism and Nutrition SOC	5 (12.5%)	1 (3.7%)	2 (6.9%)	3 (5.4%)
Fluid Retention	0	1 (3.7%)	1 (3.4%)	2 (3.6%)
Hypercalcaemia	0	0	0	0
Hyperkalaemia	0	0	0	0
Hypokalemia	2 (5.0%)	0	0	0
Hypomagnesaemia	1 (2.5%)	0	0	0
Renal and Urinary Disorders SOC	2 (5.0%)	1 (3.7%)	1 (3.4%)	2 (3.6%)
Proteinuria	1 (2.5%)	0	0	0
Vascular Disorders SOC	0	1 (3.7%)	2 (6.9%)	3 (5.4%)
Hypertension	0	1 (3.7%)	2 (6.9%)	3 (5.4%)

Source: Reviewers Table Modified from Table 10.2.1A Integrated Summary of Safety

Table 90 Incidence of Selected TEAEs in Chronic idiopathic constipation Patients taking Concomitant Agents Acting on the Renin-Angiotensin System in the Treatment Period of the Phase 3 Double Blind Placebo Controlled Trials (Group 1) Safety Population

TEAE SOC (Preferred Term)	Placebo N=56	Linaclotide		
		145 µg/day N=61	290 µg/day N=53	Linaclotide Total N=114
	n (%)	n (%)	n (%)	n (%)
Patients with at least one TEAE	33 (58.9%)	41 (67.2%)	26 (49.1%)	67 (58.8%)
Cardiac disorders SOC	4 (7.1%)	1 (1.6%)	0	1 (0.9%)
Atrial fibrillation	2 (3.6%)	0	0	0
Palpitations	1 (1.8%)	0	0	0
First Degree AV Block	1 (1.8%)	0	0	0
Sinus tachycardia	0	1 (1.6%)	0	1 (0.9%)
Gastrointestinal Disorders SOC	13 (23.2%)	17 (27.9%)	11 (20.8%)	28 (24.6%)
Diarrhea	5 (8.9%)	15 (24.6%)	4 (7.5%)	19 (16.7%)
Flatulence	2 (3.6%)	1 (1.6%)	3 (5.7%)	4 (3.5%)
Abdominal distension	1 (1.8%)	1 (1.6%)	2 (3.8%)	3 (2.6%)
Nausea	2 (3.6%)	1 (1.6%)	2 (3.8%)	3 (2.6%)
Abdominal tenderness	1 (1.8%)	1 (1.6%)	0	1 (0.9%)
Abdominal pain	1 (1.8%)	0	1 (1.9%)	1 (0.9%)
Abdominal pain upper	1 (1.8%)	2 (3.3%)	0	2 (1.8%)
Frequent bowel movements	0	0	0	0
Fecal incontinence	0	2 (3.3%)	0	2 (1.8%)
Investigations SOC	2 (3.6%)	5 (8.2%)	5 (9.4%)	10 (8.8%)
Metabolism and Nutrition SOC	2 (3.6%)	3 (4.9%)	2 (3.8%)	5 (4.4%)
Fluid Retention	0	0	0	0
Dehydration	0	0	1 (1.9%)	1 (0.9%)
Hypercalcaemia	0	0	0	0
Hyperkalaemia	0	0	0	0
Hypokalemia	0	0	1 (1.9%)	1 (0.9%)
Hypomagnesaemia	1 (1.8%)	0	0	1 (0.9%)
Hypoglycemia	1 (1.8%)	0	0	1 (0.9%)
Hyperglycemia	0	1 (1.6%)	0	1 (0.9%)
Renal and Urinary Disorders SOC	1 (1.8%)	2 (3.3%)	2 (3.8%)	4 (3.5%)
Proteinuria	0	0	0	0
Hematuria	1 (1.8%)	0	0	0
Vascular Disorders SOC	1 (1.8%)	3 (4.9%)	4 (7.5%)	7 (6.1%)
Hypertension	1 (1.8%)	3 (4.9%)	3 (5.7%)	6 (5.3%)
Orthostatic Hypotension	9	0	1 (1.9%)	1 (0.9%)

Source: Reviewers Table Adapted from Table 10.2.1B Applicants Integrated Summary of Safety pp 13144 - 13159

Table 91 Incidence of Selected Treatment Emergent Adverse Events in Chronic idiopathic constipation Patients Taking Concomitant PPIs during 12 week Treatment Period of Phase 3 Double-Blind Placebo Controlled Trials

TEAE SOC (Preferred Term)	Placebo N=61	Linaclotide		
		145 µg/day N=57	290 µg/day N=67	Linaclotide Total N=124
	n (%)	n (%)	n (%)	n (%)
Patients with at least one TEAE	42 (68.9%)	41 (71.9%)	35 (52.2%)	76 (61.3%)
Cardiac disorders SOC	2 (3.3%)	2 (3.5%)	0	2 (1.6%)
Gastrointestinal Disorders SOC	22 (36.1%)	22 (38.6%)	19 (28.4%)	41 (33.1%)
Diarrhea	6 (9.8%)	16 (28.1%)	10 (14.9%)	26 (21.0%)
Flatulence	8 (13.1%)	2 (3.5%)	0	2 (1.6%)
Abdominal distension	5 (8.2%)	2 (3.5%)	1 (1.5%)	3 (2.4%)
Nausea	5 (8.2%)	2 (3.5%)	2 (3.0%)	4 (3.2%)
Abdominal tenderness	0	0	1 (1.5%)	1 (0.8%)
Abdominal pain	3 (4.9%)	1 (1.8%)	4 (6.0%)	5 (4.0%)
Abdominal pain upper	0	4 (7.0%)	1 (1.5%)	5 (4.0%)
Frequent bowel movements	0	0	0	0
Fecal incontinence	1 (1.6%)	1 (1.8%)	1 (1.5)	2 (1.6%)
Investigations SOC	3 (4.9%)	5 (8.8%)	1 (1.5%)	6 (4.8%)
Metabolism and Nutrition SOC	4 (6.6%)	2 (3.5%)	1 (1.5%)	3 (2.4%)
Fluid Retention	0	0	0	0
Dehydration	0	0	0	0
Hypercalcaemia	0	0	0	0
Hyperkalaemia	0	0	0	0
Hypokalemia	1 (1.6%)	0	0	0
Hypomagnesaemia	0	0	0	0
Hypoglycemia	0	0	0	0
Hyperglycemia	0	1 (1.8%)	0	1 (0.8%)
Renal and Urinary Disorders SOC	1 (1.6%)	1 (1.8%)	1 (1.6%)	2 (1.6%)
Vascular Disorders SOC	0	3 (5.3%)	0	3 (2.4%)
Hypertension	0	3 (5.3%)	0	3(2.4%)
Orthostatic Hypotension	0	0	0	0

Source: Reviewers Table Adapted from Table 10.2.1C Applicants Integrated Summary of Safety pp 13160 - 13176

Table 92 Incidence of Selected Treatment Emergent Adverse Events in Chronic idiopathic constipation Patients taking Concomitant Laxatives and Mineral Supplements during the Treatment Period of the Phase 3 Placebo-Controlled Double-Blind Trials (Group 1) Safety Population

TEAE SOC (Preferred Term)	Placebo N=36 n (%)	Linaclotide		
		145 µg/day N=46 n (%)	290 µg/day N=29 n (%)	Linaclotide Total N=75 n (%)
Patients with at least one TEAE	23 (63.9%)	29 (63.0%)	17 (58.6%)	46 (61.3%)
Cardiac disorders SOC	2 (5.6%)	0	0	0
Atrial fibrillation	2 (5.6%)	0	0	0
Gastrointestinal Disorders SOC	8 (22.2%)	16 (34.8%)	11 (37.9%)	27 (36.0%)
Diarrhea	3 (8.3%)	7 (15.2%)	7 (24.1%)	14 (18.7%)
Flatulence	1 (2.8%)	3 (6.5%)	3 (10.3%)	6 (8.0%)
Abdominal distension	0	1 (2.2%)	2 (6.9%)	3 (4.0%)
Nausea	2 (5.6%)	3 (6.5%)	0	3 (4.0%)
Abdominal tenderness	0	0	0	0
Abdominal pain	0	1 (2.2%)	3 (10.3%)	4 (5.3%)
Abdominal pain upper	0	3 (6.5%)	0	3 (4.0%)
Frequent bowel movements	0	0	0	0
Fecal incontinence	0	1 (2.2%)	0	1(1.3%)
Investigations SOC	2 (5.6%)	3 (6.5%)	2 (6.9%)	5 (6.7%)
Metabolism and Nutrition SOC	1 (2.8%)	1 (2.2%)	2 (6.9%)	3 (4.0%)
Hypokalemia	0	0	1 (3.4%)	1 (1.3%)
Hypomagnesaemia	0	0	0	0
Hyponatremia	0	1	0	1 (1.3%)
Renal and Urinary Disorders SOC	1 (2.8%)	0	0	0
Proteinuria	0	0	0	0
Hematuria	1 (2.8%)	0	0	0
Vascular Disorders SOC	0	1 (2.2%)	1 (3.4%)	2 (2.7%)
Hypertension	0	0	0	0
Orthostatic Hypotension	0	0	0	0

Source: Reviewers Table Adapted from Table 10.2.1D Applicants Integrated Summary of Safety pp 13177 - 13192

There were no other notable differences in occurrence of other treatment emergent adverse events or potentially clinically significant laboratory values between patients taking the selected concomitant medications and those not taking concomitant medications.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Although there were no formal clinical trials to assess the carcinogenic effects of Linaclotide, the carcinogenic potential of Linaclotide was assessed in nonclinical studies involving rats and mice. (The reader is referred to the nonclinical review of Dr. Yuk-Chow Ng for additional details.) The results of the nonclinical studies did not demonstrate any evidence of Linaclotide induced neoplasias.

7.6.2 Human Reproduction and Pregnancy Data

Per protocol pregnant and lactating women were excluded from enrollment in the clinical development program. At the time of enrollment, females of childbearing potential were required to have a negative serum pregnancy and to be on an effective method of birth control before and during trial participation. Patients who became pregnant during the course of the clinical program, were to be taken off of investigational product and followed through to outcome.

There were 24 cases of women who became pregnant while on investigational treatment. According to the applicant, 5 were lost to follow-up and 5 were due to deliver after database lock on October 11, 2010. An additional 7 pregnancies were reported after the initial database lock. There were 6 women who became pregnant during the double-blind placebo controlled trials. Two of these women were taking Linaclotide and the other 4 were taking placebo. Most of the pregnancies occurred in the open-label long term trials. As of June 2011, there were 13 healthy babies born to mothers who had taken a trial treatment. The outcomes of the known pregnancies are presented in the table below.

Table 93 Pregnancy Outcomes in Patients Receiving Investigational Product During the Linacotide Clinical Development Program

AE Report Number	Trial Number	Age (yrs)	Patient ID	Days on IP	Investigational Product	Pregnancy Outcome
Ectopic Pregnancies						
1000003858*	MCP-103-303	40	0103011	84 days	Linacotide	Surgery
1000005603	LIN-MD-02	27	0770127	13 days	Linacotide	Surgery
Abortions						
1000013249	MCP-103-302	18	0692034	85 days	Placebo	Elective abortion
1000011158	MCP-103-302	44	0612015	87 days	Linacotide	Elective abortion
1000007615	LIN-MD-02	30	0300115	13 days	Linacotide	Elective abortion
1000012544	MCP-103-305	40	0103017	370 days	Linacotide	Elective abortion
1000013677	MCP-103-305	30	0632001	272 days	Linacotide	Elective abortion
1000016791	MCP-103-305	38	0923014	454 days	Linacotide	Spontaneous abortion
1000017615	LIN-MD-02	30	0130104	550 days	Linacotide	Elective abortion
Healthy Babies						
1000006220*	LIN-MD-01	26	0050115	65 days	Placebo	Term 3.6 kg girl ^a
1000011732	MCP-103-302	19	1282009	147 days	Placebo	Term 2.7 kg boy; Apgar 9/9
1000003855	MCP-103-305	41	0095003	101 days	Linacotide	Term 3.9 kg girl; Apgar 8/9
1000007151	LIN-MD-02	28	0750108	80 days	Linacotide	C-Section; 3.0 kg boy
1000007618	MCP-103-305	28	0873009	1 day	Linacotide	Term 2.3 kg girl; Apgar 9/9
1000009945	LIN-MD-02	30	0723112	4 days	Linacotide	Term 3.2 kg boy; Apgar 9/9
1000011242	MCP-103-305	21	0723023	187 days	Linacotide	Term 3 kg boy ^a
1000013960	MCP-103-302	22	1242013	82 days	Placebo	Term 3.5 kg boy; Apgar 5/6 ^b
1000015999	MCP-103-305	23	0602005	181 days	Linacotide	Term 3.0 kg girl; Apgar 9/9
1000015373	MCP-103-305	22	0662010	64 days	Linacotide	Term 3.7 kg girl; Apgar 8/9
1000016355	LIN-MD-02	36	1233125	172 days	Linacotide	Term 3.6 kg girl ^a
1000016993	MCP-103-305	28	1013011	500 days	Linacotide	C-Section; Term 2.7 kg boy; Apgar 9/9
1000017818	LIN-MD-02	20	0633114	353 days	Linacotide	Term 3.2 kg girl ^a
Due Dates in Future						
1000018583	LIN-MD-02	31	0493104	364 days	Linacotide	Not applicable
1000020080	MCP-103-305	35	0202007	393 days	Linacotide	Not applicable
1000020624	MCP-103-305	25	0662029	186 days	Linacotide	Not applicable
1000021193	MCP-103-305	34	0452004	402 days	Linacotide	Not applicable
Lost to Follow-up						
1000009862	MCP-103-305	22	0092017	21 days	Linacotide	Not available
1000011297	LIN-MD-02	30	1283120	41 days	Linacotide	Not available
1000012301	MCP-103-305	24	0102034	106 days	Linacotide	Not available (pregnancy not confirmed)
1000014427	LIN-MD-02	23	0073116	189 days	Linacotide	Not available
1000014548	MCP-103-305	31	0882014	42 days	Linacotide	Not available

Source: Applicant's 120-Day Safety Updated Dated November 29, 2011 pages 59 – 60.

IP = investigational product. * = Pivotal Phase 3 Double-Blind Placebo Controlled Trial in Patient with Chronic Constipation

a: Apgar Score not available. b: Apgar score at 10 minutes was 8.

In nonclinical trials, fetal harm was only demonstrated at high Linaclotide doses that resulted in material toxicity. (See the review of Dr. Ng) Given the lethality signal in juvenile mice, a Maternal Health consult was solicited to assist in evaluating the pregnancy and lactation data. According to the consultant, when animal data are available, only the presence or absence of the drug in milk is considered relevant. There are no data available on the excretion of Linaclotide or its active metabolite in human milk; however, drug levels would be anticipated to be very low and likely not detectable in human milk due to the minimal absorption and low systemic availability of Linaclotide.

7.6.3 Pediatrics and Assessment of Effects on Growth

There have been no clinical trials conducted in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The reader is also referred to the clinical pharmacology review of Dr. Sandhya Apparaju for additional information. Single doses of Linaclotide up to 2897 μ g (approximately 10-fold higher than the proposed high dose to be marketed) were given to healthy volunteers and tolerated well with no consequences other than diarrhea. Doses up to 966 μ g were given per protocol for up to 7 days in Phase 2 trials. There were no known instances of intentional overdose and cases of purposeful drug abuse.

The 4-week Randomized-Withdrawal (RW) phase of Trial MCP-103-303 was designed to assess the drugs potential to cause rebound worsening of constipation symptoms and withdrawal symptoms. During the RW period, patient who had been taking either the 145 μ g or 290 μ g dose of Linaclotide were re-randomized to receive placebo or continue Linaclotide treatment with the same dose. Patients who were initially on placebo during the treatment period were given 4 weeks of Linaclotide 290 μ g. The reader is referred to Section 5.3.3.2 of this review. There was no evidence of withdrawal effects or a rebound worsening of constipation symptoms relative to baseline after Linaclotide treatment was withdrawn.

7.7 Additional Submissions / Safety Issues

7.7.1 Ischemic Colitis

Laxatives are among the pharmacological agents known to be associated with ischemic colitis.³² Because of this, an in-depth analysis was performed to assess for a possible association between Linaclotide and ischemic colitis.

7.7.1.1 Overview of Ischemic Colitis

Intestinal (mesenteric) ischemia can be classified into three types based on the rapidity and extent of disruption of the blood supply: acute mesenteric ischemia, chronic mesenteric ischemia (intestinal angina), and colonic ischemia (ischemic colitis).³¹ Colonic ischemia is the most encountered form of gastrointestinal ischemia, accounting for approximately 50 -60% of gastrointestinal ischemic cases. It is estimated that ischemic colitis accounts for 1 in 1000 - 2000 hospitalizations, but its incidence is often underestimated.^{31, 32} Ischemic colitis may be further subclassified into gangrenous and non-gangrenous forms.^{32,33} In 1992 Brandt and Boyley developed a classification of ischemic colitis which seems to have been adopted by the American Gastroenterological Association.^{15,34} This classification scheme states that colonic ischemia is a spectrum of disorders and is categorized (based on severity and clinical presentation) as follows: (1) reversible colopathy (submucosal or intramural hemorrhage) (2) transient colitis, (3) chronic colitis, (4) stricture, (5) gangrene and (6) fulminant universal colitis.^{15,32}

Ischemic colitis (including drug-induced ischemic colitis) develops when blood flow to a part of the large intestine is diminished leading to colonic inflammation and in some cases, permanent colon damage. Although there is a gangrenous form of ischemic colitis that may result in high mortality if not treated, most patients have self-limiting mild or transient, nongangrenous disease. Consequently, the incidence of ischemic colitis is often underestimated because most patients do not seek medical help or are not hospitalized; hence they are not included in case report series.³²

The initial ischemic insult in the transient form may occur days or weeks prior to the development of symptoms.³¹ Most cases of ischemic colitis do not have a recognizable cause, although cases have been associated with systemic hypoperfusion, surgical disruption of blood flow following major vascular surgery, colon cancers, and obstructive lesions of the gastrointestinal lumen.³² Colonic ischemia has also been associated with various medications, long-distance running, coagulopathies (e.g. Protein C deficiency, Protein S deficiency), hypotension and hypovolemia, chronic constipation, and vasospasm.¹⁵ Medications may induce ischemic colitis by producing vasoconstriction; vasculitis; decreasing splanchnic flow via systemic hypotension; or promotion of thrombosis from hormonal effects.³⁵ "Increased intracolonic pressure due to impacted feces or enema injury has also been linked to the development of colonic ischemia."³⁵ Case reports of ischemic colitis

following colonoscopy have also suggested that increased intracolonic pressure from air insufflation or glutaraldehyde may induce ischemic colitis.³⁵

There are a number of conditions that may predispose one to ischemic colitis including strenuous physical activity, dehydration, illicit drug use, risk factors for heart disease, increased age, and history of vasculopathy. Most cases of ischemic colitis occur in the elderly.¹⁵ One study showed that a clinical presentation of lower abdominal pain with or without bloody stool was 100% predictive of ischemic colitis when accompanied by four or more of the following risk factors: age over 60, hemodialysis, hypertension, hypoalbuminemia, diabetes mellitus, or constipation-inducing medications.³⁶

Patients with ischemic colitis are often misdiagnosed despite increased awareness of the condition.^{15,32} This may be attributed to the nonspecific clinical presentation which varies depending on the severity and extent of the disease. Common signs and symptoms include rapid onset of abdominal pain, tenderness or cramping usually localized over the affected area of bowel, which in most cases is the lower left side of the abdomen.^{15,37} (Signs and symptoms of right-sided lesions may also occur and are usually associated with a higher risk of severe complications.)¹⁵ Patients may also have hematochezia, bloody stools, urgency, nausea, vomiting, and diarrhea.^{15,37} Hematochezia usually develops within one day of the onset of pain. The bleeding often not profuse and does not cause hemodynamic instability or require transfusion.

The diagnosis of ischemic colitis requires a high index of clinical suspicion because there are many forms of colitis (e.g. infectious colitis, colitis secondary to radiation therapy) and other organic conditions (inflammatory bowel disease, diverticulitis) that may mimic ischemic colitis.^{15,32} The presence of diarrhea, abdominal pain and/or tenderness, and mild lower gastrointestinal bleeding even in the absence of risk factors should prompt consideration of ischemic colitis in the differential diagnosis.³² All patients with clinical suspicion for IC should have stool cultures for bacteria and should have other common clinical conditions ruled out. There are no laboratory markers that are specific to ischemic colitis.³² Patients may have elevated lactate, LDH, CPK, amylase, alkaline phosphatase and white count levels.^{14,15,31,32}

Barium enema was the first method used to diagnosis ischemic colitis but has been replaced over the past 25 years with colonoscopy as the diagnostic modality of choice in patients who have no signs of peritonitis.^{15,32,33} Colonoscopy allows visualization of the colonic mucosa and tissue sampling for histology.^{32,33} (Note: With the exception of colonic gangrene, neither endoscopic nor histological findings are specific and both are highly dependent on the duration and severity of ischemic injury.)^{32,33} Diagnosis of ischemic colitis requires early colonoscopy (<48 hours) and serial studies are required to establish the diagnosis.³² Plain abdominal x-ray may reveal nonspecific findings such as thumb-printing, air-filled loops, mural thickening, aperistalsis, or intraabdominal air secondary to perforation. Sonography has been reported to aid in diagnosis but is less widely used. Mesenteric angiography usually has no role in the evaluation of ischemic colitis because by the time of presentation, colon blood flow has returned to normal.³³ Angiography may be indicated in the diagnosis of acute mesenteric ischemia either because only the right side of the colon is affected or because the

patient has severe physical findings that are disproportionate to what is normally seen in ischemic colitis. A CT scan usually only demonstrates nonspecific findings.

Management of ischemic colitis depends on the severity of illness. Eighty five percent of cases managed conservatively will show improvement within 1 to 2 day with complete resolution of symptoms within 1 or 2 weeks.¹⁵

7.7.1.2 Drug-Induced Ischemic Colitis

Although long-term and life-threatening complications of ischemic colitis are possible, most patients with drug-induced ischemic colitis develop the transient nongangrenous form which resolves with few (if any) sequelae provided that the offending agent(s) is(are) discontinued early in the course of the disease.³⁵ 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.¹⁴ Attribution of the event to the drug is further complicated by the fact that the initial ischemic insult may occur days or weeks prior to the development of symptoms.³¹ The management of drug-induced ischemic colitis is similar to management of ischemic colitis from any other cause except that offending agents must be discontinued. Medical management is conservative with intravenous fluids, hemodynamic stabilization, bowel rest, avoidance of vasoconstrictive drugs, and empiric antibiotics (in severe cases). Surgical intervention is only required for those patients who develop complications.

7.7.1.3 Submission specific assessment of Ischemic Colitis

Three cases of ischemic colitis were reported during the clinical development program of Linaclotide for IBS-C and CC. One was reported as an adverse event in a Phase 2 CIC trial. The patient was discontinued from the trial due to lack of efficacy 11 days prior to development of the ischemic colitis. The other 2 cases were reported in IBS-C patients receiving Linaclotide in the open-label long-term safety trials.

Because of the aforementioned issues related to the diagnosis of ischemic colitis and the often transient nature of the disease, it seems to be almost impossible retrospectively to determine with any degree of certainty whether or not Linaclotide use causes ischemic colitis. To do so would require at least the following:

- 1) a definitive diagnosis of ischemic colitis could be established based on the clinical evidence {including but not limited to patient reported symptoms and objective findings including clinical signs, endoscopic findings, and possibly histological findings as provided in the case report forms}
- 2) a probable causal relationship between the drug and development of the condition was evidenced by demonstrating a 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
- 3) exclusion of other causes of ischemic colitis.

The detection of a signal for ischemic colitis with this particular application is further complicated by the fact that both IBS and constipation, independently, are risk factors for developing ischemic colitis.^{31,32,34,38} For this particular application, a review of the dataset showed that patients with Chronic idiopathic constipation experienced a slightly higher incidence of adverse events consistent with rectal hemorrhage. (See table below created by the Statistician).

Table 94 Comparison of Rectal Bleeding in IBS-C and CIC Patients

	Linaclotide		
	Patients in the Chronic idiopathic constipation Trials	Patients in the IBS-C Trials	All Linaclotide Patients in Phase 2 and 3 trials.
# of Patients	1627	2753	4370
Reports of Hematochezia	12 (0.74%)	8 (0.29%)	20 (0.46%)
Reports of Melena	1 (0.06%)	1 (0.04%)	2 (0.05%)
Reports of Rectal Hemorrhage	17 (1.04%)	19 (0.69%)	36 (0.82%)
Rectal Bleeding Total	30 (1.84%)	28 (1.01%)	58 (1.33%)

Source: Table generated by Statistical Reviewer.

Therefore, In an attempt to assess if there was a possible increased risk of ischemic colitis associated with Linaclotide use in the CIC population, the applicants adverse event dataset from the Phase 2, Phase 3, and long-term safety trials was reviewed to determine if there was an imbalance in the number of patients reporting adverse events consistent with rectal bleeding. The following table generated by the statistician, shows the results of that analysis for the CIC population.

Table 95 Incidence of Reports of Rectal Bleeding in Chronic Idiopathic Constipation Patients

	Placebo	Linaclotide doses			Total
		145µg	290µ	Any dose	
#Patients	423	430	422	852	1275
Reports of Hematochezia	4 (0.95%)	1 (0.23%)	6 (1.42%)	7 (0.82%)	11 (0.86%)
Reports of Melena	0 (0.0%)	1 (0.23%)	0 (0.0%)	1 (0.12%)	1 (0.08%)
Reports of Rectal Hemorrhage	3 (0.71%)	7 (1.63%)	2 (0.47%)	9 (1.06%)	12 (0.94%)
Rectal Bleeding Total	7 (1.65%)	9 (2.09%)	8 (1.90%)	17 (2.00%)	24 (1.88%)

The adverse event dataset was also reviewed for MedDRA lower level terms and preferred terms representing adverse events that may be indicative of ischemic colitis. The reviewer identified a small amount of splitting within the dataset, therefore lower level terms were combined when appropriate and mapped to preferred terms. The following illustrates the lower level terms and verbatim terms that were grouped together (and ascribed to preferred terms) for the analysis:

- Group 1) Black Stool, Blacks Stools, Black Tarry Stools, Dark Stools, Dark Stool, Intermittent Black Stool, Melena,
- Group 2) Bloody Stools, Bloody Stool, Blood in Stool, Blood on Stool, Heme Positive Stools, Hemocult Positive Stool for Occult, Intermittent Blood in Stool, Intermittent Blood with Stool, Occult Blood in Stool, Positive Hemocult Stools, Positive Hemocult, Small Blood Droplet in Bowel Movement
- Group 3) Bleeding Hemorrhoid,
- Group 4) Blood in Rectum, Blood Per Rectum, Blood From Rectum, Bright Red Blood per Rectum, Hematochezia, Rectal Bleeding, Rectal Bleeding (Worsening), Rectal Bleeding After Bowel Movements, Worsening of Rectal Bleeding, Increased Rectal Bleeding
- Group 5) Bowel Obstruction
- Group 6) Decrease in HCT, Decrease in Hemoglobin, Decrease HGB, Decreased Hematocrit. Decreased Hematocrit level, Decreased Hemoglobin, Decreased Hemoglobin 10, Decrease Hemoglobin Lab Value, Decreased Hemoglobin Level, Low Hematocrit, low Hemoglobin, Low Hematocrit, Low Hematocrit Level, Low Hemoglobin, Low HGB, Worsening Low Hematocrit, Worsening Low Hemoglobin,
- Group 7) Gastroenteritis, Gastroenteritis
- Group 8) Ischemic Colitis
- Group 9) Melanosis Coli

There was also one patient with abdominal tenderness for whom the case report form was requested. The applicant was asked to provide a listing for each of the patients with adverse events that corresponded to these terms. In addition, the applicant was also asked to provide patient ID number, site number, trial identifier where the AE of interest was observed, treatment group (i.e. placebo or dose of Linaclotide), number of days on drug, date of onset of the adverse event as well as the stop date, and an evaluation of the possibility of adverse being related to ischemic colitis. The applicant provided narrative summaries for all cases identified by the reviewer, along with their own summary analysis of all the data and an evaluation of the possibility of ischemic colitis being induced by Linaclotide. The reviewer independently reviewed all case report forms requested to assess if the cases were possibly representative of ischemic colitis and if there was a possible causal relationship with the study treatment.

Each of the case report forms associated with the pre-specified adverse events were reviewed by the primary reviewer to determine: 1) the likelihood that the adverse event was a case of ischemic colitis based on the presence or absence of abdominal pain and rectal bleeding and 2) the possibility that the adverse event was drug related. Questions the reviewer used during this assessment of each case report included:

- Did the patient experience abdominal pain and/or lower gastrointestinal or rectal bleeding?
- Are there identifiable risk factors for ischemic colitis (e.g. patient age \geq 65 years, patient history of coagulopathy, patient history of vascular disease or disease known

to be associated with vasculitis, smoking history, use of medications known to be associated with ischemic colitis)

- Can the possibility of ischemic colitis be ruled out based on the information provided in the case report form (yes/no)?
- Is there another readily identifiable cause of the adverse event? (yes/no) If yes, what is the alternative cause for the rectal bleeding and abdominal pain?
- If there was no other readily identifiable cause for the patient's symptoms, was the study medication discontinued or did the patient have a reduction in dose? Following cessation of the study medication or dose reduction, did the patient's symptoms improve or resolve?

If another readily identifiable cause of the adverse event was identified, the further review of the case ceased at that time.

The applicant was also asked to independently evaluate the Linaclotide database for evidence of potential, previously unrecognized, cases of ischemic colitis. In addition to the specific case reports requested by the reviewer, the applicant expanded the reviewer's criteria and created a second listing that included additional patients that experienced an adverse event that coded to any of the following preferred terms:

colitis ischemic, rectal hemorrhage, hematochezia, melena, feces discolored, anemia, hematocrit decreased, hemoglobin decreased, melanosis coli, hemorrhoidal hemorrhage, anal hemorrhage, occult blood positive, ileus, colitis, enteritis, gastroenteritis, viral gastroenteritis, intestinal obstruction, large intestinal obstruction, and small intestinal obstruction. There were initially 122 patients identified by the Division. Using the expanded search criteria, the applicant identified an additional 230 patients associated with the pre-specified "AEs of Interest".

After identifying the 352 patients that had "adverse events of interests", the applicant (in conjunction with consulting gastroenterologists) used the following methods to review and analyze adverse events possibly indicative of ischemic colitis and to further screen data from patients reporting these adverse events for potential signals of ischemic colitis:

- Clinical screening criteria to identify "Cases of Interest" were established.
 - The patient reported "abdominal pain" as an AE (or any other AE coding to the preferred term "abdominal pain")
 - The patient reported an AE indicative of lower GI bleeding or blood loss through the lower GI tract. These AEs included anal hemorrhage, feces discolored, hematochezia, hemorrhoidal hemorrhage, melena, occult blood positive, and rectal hemorrhage.
 - The start date of the AEs in the aforementioned criteria had to occur within 72 hours of one another. (The AEs could occur in any order. The durations of the lower GI bleeding and abdominal pain were not considered.)
- Clinically relevant data from patients with "AEs of Interest" were screened by the applicant using the clinical criteria defining "Cases of Interest"
- All available clinical safety data from each identified "Case of Interest" were provided to the expert panel of gastroenterologists for adjudication, whereby each member determined the likelihood of ischemic colitis for each of the cases.

It is important to note that for each “Case of Interest”, members of the panel were provided with all of the patient’s clinical data collected during study participation (including all AEs, laboratory test results, vital signs, electrocardiograms and concomitant medications. The patient’s treatment group was not provided. However, other clinical information (including written narratives, hospital records, MedWatch forms) were provided for use in the assessment. For each case, the panelists completed a form to 1) confirm that the case met the criteria for adjudication 2) assess the likelihood that the case was ischemic colitis and 3) for cases that were considered to be possible or probable ischemic colitis, rate the relationship of the study drug to ischemic colitis. Appendix A contains a sample of the adjudication form used by the panel to assess each case.

From the case reports submitted in response to the December 9, 2011 information request, the reviewer identified 11 “cases of interest” for additional assessment to determine whether these patients could be potential cases of ischemic colitis that were study treatment related.. The applicant identified 14 “cases of interest”. This applicant’s list included both IBS-C and CIC patients. The differences in the number of “cases of interest” identified by the reviewer versus the applicant may be attributed to slight differences in criteria used to identify “cases of interest” (i.e. the panel required that the initiation of the abdominal pain and bleeding start within 72 hours of one another.) Of the 14 “cases of interest”, the majority of the applicant’s expert review panel rated the likelihood of ischemic colitis as probable in the 3 patients. (All were previously identified by the investigators during the conduct of the trials. Of the 3, only 1 patient had chronic idiopathic constipation as the primary diagnosis.) The remaining cases were rated as insufficient evidence to support a diagnosis of ischemic colitis by the majority of members of the panel.

Of the 11 “cases of interest” identified by the reviewer, all involved the 290 mcg dose of Linaclotide. All cases were mild to moderate in intensity and there did not appear to be a temporal pattern between the initiation of study treatment and time to developing the event. Five (5) of the reviewer’s “cases of interest” were cases where the patient was able to continue on the study drug and complete the clinical trial. Four patients had a reduction in dose and 2 patients were discontinued from the clinical program. If the patient was able to continue study treatment without the recurrence of symptoms, then the analysis for ischemic colitis was stopped. Upon completion of the review of the remaining 6 cases, the reviewer identified 4 cases (patients 0053035, 061002, 0393021, and 0870101) for which the diagnosis of ischemic colitis could not definitively be ruled in or out and for which another cause of rectal bleeding could not be identified. These cases were sent to the sponsor for adjudication using the same criteria outlined in their previous submission. Of the 4 patients identified by the reviewer, one patient met the applicant’s criteria to be a “Case of Interest.” The other 3 patients identified did not meet the applicant’s criteria for “Case of Interest” but were still adjudicated. All cases were considered by all members of the Expert Panel to have insufficient evidence to support the diagnosis of IC.

The following table is the applicant’s list of CIC cases identified for adjudication. This is followed by the reviewers table of “cases of interest.”

Table 96 Applicants "Cases of Interest" for Adjudication to Assess Ischemic Colitis in Chronic idiopathic constipation Patients

Patient ID	Study in Which AE of Interest Occurred	Treatment at the time of the Adverse Event	AE(s) of Interest Reported (Preferred Terms)	Additional Case information
Patients Previously Diagnosed with IC by Study Investigators				
020007	MCP-103-201	Lin 290µg	Colitis Ischemic	This 74 year old male was enrolled in the Phase 2 study of Linaclotide. He was treated with 290mcg of Linaclotide beginning April 17, 2007. Reportedly the patient missed one dose on April 23, 2007. The last dose of study medication was taken on April 30, 2007 and the patient withdrew from the study on May 1, 2007 because of lack of efficacy. He was reported to have developed ischemic colitis on May 12, 2007. The patient was noted to have the onset of sharp severe mid-abdominal pain associated with a hard bowel movement with a small amount of bleeding per rectum approximately 10 days after the last dose of study drug. About 2 days later, after administering a Fleet's enema, he experienced dull abdominal pain associated with the passage of dark red blood. His abdominal pain persisted until he was seen by the investigator, whose impression was that ischemic colitis should be ruled out. A flexible sigmoidoscopy was performed which revealed colitis of the distal colon at about 30 -40cm. A mucosal biopsy was consistent with ischemic colitis. The patient was treated as an outpatient. A repeat colonoscopy on June 5, 2007, showed no evidence of colitis and subsequent biopsies were normal. Risk factors for ischemic colitis included age, chronic constipation, history of hyperlipidemia, and treatment with lovastatin and aspirin. The investigators assessed that there was no evidence to indicate that the short course of Linaclotide contributed to the event, especially in the presence of a number of cofounders. 5 members of the expert panel assessed this as a probable case of ischemic colitis. 1 stated that it was possibly study drug related. 4 stated that it was probably not treatment related. In the opinion of this reviewer, this is a probable case of IC that is possibly study drug related.
Patients with AEs of Interest Cited by FDA Requiring Additional Investigation				
0073001	MCP-103-303	Placebo	Viral Gastroenteritis	This patient withdrew from the study and did not receive Linaclotide. The patient was a 30 year old white female with a history of hypertension, depression, anxiety, and constipation. Concomitant medications included amlodipine with benazepril, wellbutrin XL, and hydroxyzine. The patient was hospitalized for 3 days for viral gastroenteritis after she presented with nausea, vomiting, abdominal pain, and bloody diarrhea. While in the hospital she had an elevated WBC count. A CT scan with contrast was consistent with infectious or inflammatory colitis. A flexible sigmoidoscopy revealed a normal colon with no evidence of colitis or bleeding. Stools was negative for ova and parasites, Giardia and Cryptosporidium antigen, and C. difficile toxin. She was treated with IV fluids, pain meds, and Zofran for nausea. The pt had no bloody diarrhea after admission and it was noted that she began menstruating on the day she was hospitalized.

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Patient ID	Study in Which AE of Interest Occurred	Treatment at the time of the Adverse Event	AE(s) of Interest Reported (Preferred Terms)	Additional Case information
				<p>The AE resolved on Day 6 after onset and after the patient was discharged. Note the patient took her last dose of study drug on (b) (6), the same day that she was hospitalized. The Investigator considered the SAE to be moderate in severity and possibly related to study drug. However, in the opinion of this reviewer this assessment is not valid considering objective data. Both the viral gastroenteritis and the patient's menstrual status could contribute to the bloody diarrhea. 3 members of the expert panel stated there was insufficient evidence to diagnosis ischemic colitis 2 members of the panel stated that it was a possible case of ischemic colitis. The same 2 members stated that the case was possibly study treatment related. In the opinion of this reviewer, this dose represent a possible case of IC. However, it is not probable that this is IC given normal sigmoidoscopy and other confounders which may have caused the bloody diarrhea.</p>
Patients with AEs of Interest that Met Case of Interest Criteria				
0051009	MCP-103-305	Lin 290 µg	Rectal hemorrhage	<p>This had also participated in the phase 2 trial MCP-103-201. The patient was a white female with a past history of GERD, hemorrhoids, s/p rectocele repair, migraines, asthma/allergies, bacterial overgrowth, and chronic lower back pain. Concomitant medications included Fosamax, Bisacodyl, Chondroitin with Glucosamine, Protonix, Excedrin, Combivent, and Ibuprofen. The patient was 50 years old when she experienced mild rectal bleeding that persisted from study day 187 until day 238. The investigator assessed this AE as unrelated to study drug. There is no additional information provided by the applicant. 5 members of the adjudication panel stated there was insufficient evidence to diagnosis ischemic colitis. This reviewer concurs. The patients history of hemorrhoids may account for the rectal bleeding. However, additional details are required before an true assessment can be done.</p>

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Patient ID	Study in Which AE of Interest Occurred	Treatment at the time of the Adverse Event	AE(s) of Interest Reported (Preferred Terms)	Additional Case information
0063008	MCP-103-303	Placebo	Rectal hemorrhage	This 44 year old patient experienced the AE of interest (rectal hemorrhage) while receiving placebo during the Randomized Withdrawal Period; this patient had previously received Linaclotide 145mcg during the treatment period (21 days had elapsed from the last dose of Linaclotide to the onset of the event). The investigator assessed this event as being mild in intensity and unlikely related to study. In addition to constipation, the patient had a medical history which included GERD with Erosive esophagitis, colonic polyps, COPD, sinus tachycardia, and hiatal hernia. Concomitant medications included Digoxin, Prevacid, Albuterol, and Verpamil. The patient experienced abdominal pain associated with rectal bleeding on study day 106. The event was assessed as mild and unlikely related to study drug. There was no narrative submitted with the case report form. 4 members of the adjudication panel stated there was insufficient evidence to diagnosis ischemic colitis. 1 member of the stated that this was a possible case of ischemic colitis that is possibly related to study drug. This reviewer believes that this is possibly a case of ischemic colitis, although it is not probable.
0393021	MCP-103-305	(Lin 290 µg) Lin 145 µg	Feces discolored	This patient reported the AE of interest while receiving Linaclotide 145mcg during the long-term open label trial. The patient had previously received a Linaclotide dose of 290mcg during the first 38 days of the trial, but was down-titrated to the 145mcg dose for the remainder of the trial due to diarrhea. The patient was a 45 year old white female with an extensive past medical history that included colonic polyps, hematochezia, hemorrhoids, hyperlipidemia, and overweight. The patient experienced intermittent black stool (faeces discolored) assessed as moderate in intensity and possibly related to study medication by the investigator. The episodes of intermittent black stool occurred simultaneously with diarrhea that was assessed as moderate in intensity and possibly study drug related. There was no narrative submitted for this patient. All 5 members of the panel stated there was insufficient evidence to establish a diagnosis of IC. In the opinion of this reviewer, this is a possible case of IC but not a probable case. The patient has a history of hematochezia, colonic polyps, and hemorrhoids, all of which may contribute to the event of interest. Additional data would be required before an assessment could be done.

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Patient ID	Study in Which AE of Interest Occurred	Treatment at the time of the Adverse Event	AE(s) of Interest Reported (Preferred Terms)	Additional Case information
0693003	MCP-103-303	(Lin 290 µg) Placebo	Rectal hemorrhage	This patient reported the AE of interest while receiving placebo during the randomized withdrawal period for the trial. The patient had previously received Linaclotide 290mcg during the treatment period (14 days had elapsed from the last dose of Linaclotide to the onset of the event.) The patient was a 55 year old white female with a history of GERD, Depression, and Mitral Valve Prolapse. Concomitant medications included aspirin, lexapro, estradiol patch, metoprolol, and omeprazole. The patient experienced rectal hemorrhage assessed by the investigator as mild and unlikely related to study drug. There was no narrative presented with this case report form. All 5 members of the adjudication panel stated there was insufficient evidence to establish the diagnosis of IC. The patient has a history of estradiol use which places her at increased risk of coagulopathy, a known risk factor for developing IC. It is possible that this is a case of IC, however this reviewer agrees that more data is required.

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Table 97 Reviewers Cases of Interest in the Assessment of Ischemic Colitis

Patient ID	Study in Which AE of Interest Occurred	Treatment at the time of the Adverse Event	AE(s) of Interest Reported (Preferred Terms)	Additional Case information
002007	MCP-103-302	Lin 290 µg	Colitis Ischemic	This case was also identified by the sponsor. Please refer to the preceding table for additional details.
870101	LIN-MD-02	Lin 290 µg	Faeces Discolored	This case was a 66 year old white female who had been taking 290mcg of Linaclotide during the Phase 3 Double Blind trial and the long-term safety trial. This patient was s/p myocardial infarction and cerebrovascular accident. She also had a history of fibromyalgia, asthma, and allergies. Concomitant medications included Acyclovir, Calcium+Vitamin D, Celecoxib, Estradiol, Ipratropium, Omeprazole, Advair and Echinacea. On July 14, 2009, 139 days after starting the study drug, the patient developed a gastroenteritis described as moderate in intensity by the investigator. The patient also experienced black stools for 14 days and appear to have resolved spontaneously. However, the gastroenteritis was described as ongoing. The investigator assessed the events as unrelated to study drug. On July 30, 2009, the patient began to experience watery diarrhea which was assessed as possibly related to study drug. Consequently the patients dose of the study drug was decreased to 145mcg and she was able to complete the long-term trial. In the opinion of this reviewer, it is possible that the patient had a transient case of ischemic colitis, however, more information would be required to make a definitive diagnosis. The patient has risk factors which include her age, use of estradiol, and history of vascular disease. While it is possible that this event was study drug related, in the opinion of the reviewer this is unlikely. Even though the patient reported black stools, gastroenteritis, and abdominal pain, the applicant did not consider this to be a Case of Interest because the cause of the black stools had an alternative explanation (bismuth which was started on trial Day 139). Additionally, the onset of the abdominal pain did not occur within 72 hours of the onset of the black stools. All five expert panelists considered this case to have insufficient evidence for IC.
713002	MCP-103-303 MCP-103-305	Lin 290 µg	Hematochezia Hemoglobin Decreased	This patient was a 32 year old white male with a history of GERD, dyspepsia, and left rotator cuff injury. The patient was taking 290mcg of Linaclotide during the Phase double blind and long-term trial. On study day 98, the patient developed mild hematochezia which initially resolved spontaneously but then reappeared on study day 100. The hematochezia persisted through day 45 of the long-term trial. (a total of 57 days.) The patient's hemoglobin also decreased during this time. The investigator assessed this case as unrelated to study drug and no action was taken with regard to study treatment. Reportedly the hematochezia resolved spontaneously without sequelae. There was no additional diagnostic work-up to assess for the cause of the hematochezia. In the opinion of the reviewer, this is a possible case of ischemic colitis. However, additional evidence would be required to make a definitive diagnosis. It is also possible that this is study drug

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				related. However, there was never a dechallenge of study treatment.
583005	MCP-103-303	Lin 290µg	Feces Discolored/Black Stool	This is a 52 year old white female with a history of tachycardia, allergies, hypercholesterolemia, tobacco use, breast cancer, osteopenia, fibromyalgia, osteoarthritis, migraines and decreased CD4 count. Concomitant medications included Meloxicam, Fish Oil, Paroxetine, Alprazolam, Claritin, Multivitamin, Simvastatin, Chlorzoxazone. On Study day 67, the patient developed diarrhea assessed as moderate in intensity and probably study drug related. On study day 72, the patient developed dark stool which persisted until study day 75. This was also assessed as being moderate in intensity and probably related to study drug. There did not appear to be any additional work-up done to assess the dark stools. While it is possible that this was a case of ischemic colitis, additional information would be required prior to diagnosis. The patient was able to complete the double blind and long-term study.
0243007	MCP-103-3003	Lin 290µg	Rectal Hemorrhage	This was a 35 year old white male with a history of internal hemorrhoids, hematochezia, and prior shoulder injury. On study day 24, the patient developed moderate diarrhea and rectal bleeding. This persisted until study day 27. The investigator assessed the diarrhea as possibly being related to study drug. However, the rectal bleeding was assessed as unlikely related to study drug. There did not appear to be any additional work-up for this patient and there was no narrative provided for this case. It appears that the event resolved spontaneously with no sequelae. The patient was able to complete the trial. The patient has a history of internal hemorrhoids and hematochezia which may account for the patients rectal hemorrhage. While it is possible that this event is a case of ischemic colitis, in the opinion of the reviewer it is unlikely.
0145001 (also referred to as patient 061002 in trial MCP-103-201)	MCP-103-305	Lin 290 µg	Hematochezia/Blood in stool	This was a 60 year old female with medical history that includes osteoarthritis, neuroma to bilateral lower extremities, gall bladder disease, varicose veins, and herpes zoster. Past medical history appeared otherwise insignificant for cardiovascular disease. Concomitant medications included Fosamax, Mylanta, Calcium, and Vitamin D. The patient was taking 290mcg of study drug when she experienced abdominal discomfort described as moderate intensity. This resulted in a dose Reduction. Approximately 28 days later, on trial day 37, the patient experienced mild hematochezia. The hematochezia appears to have resolved spontaneously on the same day. However, during this time it appears that the patient also complained of moderate incomplete evacuation which lasted from 12/6/08 until 1/1/09. Treatment was temporarily held and subsequently the dose of the study drug was decreased. These events were

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				<p>assessed as possibly related to study drug. There does not appear to have been a diagnostic work-up associated with the event. Because of the patient's age and history of constipation, she is an increased risk of developing ischemic colitis. While it is possible, that this represents a mild case of IC, in the opinion of this reviewer, it is not probable. This patient did not meet our criteria to be a Case of Interest by the applicant because she did not have an AE of abdominal pain. The applicant maintains that even if we were to consider the patient's abdominal discomfort as synonymous with abdominal pain, the patient would still not be a Case of Interest because the start date of the lower GI bleeding patient occurred 34 days after the start date of the abdominal discomfort. All five expert panelists considered this case to have insufficient evidence for IC.</p>
0053035	MCP-103-305	Lin 290 µg	Rectal hemorrhage	<p>This 30-year-old white female with a history of constipation, hematochezia, migraines and allergies. She was not on any concomitant medications. According to the information presented by the applicant, the patient did not report any AEs during MCP-103-303 (where she received Linaclotide 145 mcg during the Treatment Period and placebo during the Randomized Withdrawal Period). During this long-term trial, the patient reported rectal hemorrhage (investigator term: bright red blood per rectum) on Days 3 to 11 of MCP-103-305. The patient did not report abdominal pain or discomfort as AEs, but did report diarrhea (investigator term: diarrhea) on Days 352 to 370. Although, this patient appears to have no risk factors for IC, there have been cases of IC in younger adults following treatment with laxatives. According to the applicant, the diarrhea, not the rectal hemorrhage was associated with a dose reduction. It is possible that the rectal hemorrhage was a mild transient case of ischemic colitis. However, additional information would be required to make a definitive diagnosis. Even though the patient had evidence of lower GI bleeding, the Sponsor did not consider this to be a Case of Interest because the patient did not report abdominal pain as a concurrent AE. All five expert panelists considered this case to have insufficient evidence for IC.</p>
0093006	MCP-103-303	Lin 290µg	Hematochezia	<p>This was a 39 year old white female with a history that included allergies, depression, irregular menses, and lower back pain. Concomitant medications included docusate, St. John's Wort, loratadine, natural and semisynthetic estrogens, and vitamins. On study day 51, the patient experienced mild hematochezia and mucousy stools assessed as possibly study drug related by the investigator. There was no additional work-up. The patient's use of estrogens place her at increased risk of coagulopathy and IC. In the opinion of this reviewer, IC is possible but not probable and there is insufficient evidence to support the IC diagnosis. The patient was also able to continue to the study drug and the trial. Therefore it is also unlikely that this was caused by the study drug. Of note, this patient was subsequently discontinued from the clinical program following an emergent</p>

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Patient ID	Study in Which AE of Interest Occurred	Treatment at the time of the Adverse Event	AE(s) of Interest Reported (Preferred Terms)	Additional Case information
				hospitalization and surgery for a perforated diverticulum.
0393021	MCP-103-303	Lin 290 µg	Abdominal Pain Feces discolored	This is the case of a 45 year old white female with a history that includes depression, allergies, ADHD dyspepsia, colonic polyps, hemorrhoids, and hematochezia. Concomitant medications included Bupropion, Duloxetine, Methylphenidate, and Tylenol. The patient is also s/p polypectomy. The patient was initially on 145mcg of Linaclotide in the double-blind trials. She was subsequently rolled over into the long-term trial and began taking 290 mcg of the study drug. Approximately 32 days after the study drug, the patient developed diarrhea which resulted in a dose reduction. The patient later developed right upper quadrant abdominal pain (moderate intensity), diarrhea and intermittent black stools which persisted from Day 144 to 177 of the long-term safety trial. It was also noted that during this time there was an increased blood pressure and pulse reading (which in the absence of additional data may have been indicative of an occult bleed). In the opinion of this reviewer, it is possible that this is a case of IC, but additional information would be required to make the diagnosis because of the patient's past medical history. The applicant considered this to be a Case of Interest and had it adjudicated by the Expert Panel. All five panelists considered the case to have insufficient evidence for IC.
0370104	LIN-MD-01 LIN-MD-02	Lin 290µg	Rectal hemorrhage	This is the case of a 71 year old male with chronic constipation, GERD, coronary artery disease, hypercholesterolemia, hypertension, and anxiety. The patient is also s/p coronary artery bypass. Concomitant medications included Rosuvastatin, Zegerid, Papaverine, Lisinopril, Hydrochlorothiazide, NEXIUM, and Multivitamins. This patient was previously enrolled in Trial LIN-MD-01 and was treated with placebo during the treatment period. On study day 44, the patient developed rectal hemorrhage which was mild in intensity and assessed as unrelated to treatment. The symptoms persisted for 3 days. But there is not indication of a diagnostic work-up being done. The patient was able to complete the double blind study and was carried over into the long-term safety trial where he was started on the 290mcg dose of Linaclotide. On June 4, 2009 (Study Day 4), the patient experienced the AE of diarrhea. The diarrhea resolved on Jun 07, 2009, 2 days after Linaclotide discontinuation. The Investigator considered the AE of diarrhea to be severe in intensity and probably related to Linaclotide. On June 12, 2009 the patient developed rectal bleeding which persisted for 16 days. The investigator assessed the rectal bleeding as mild in intensity and probably related to study drug. Again, there did not appear to be a work-up for IC. This patients age and medical history of vascular disease and constipation place him at increased risk of ischemic colitis. In the opinion of the reviewer, it is possible that this was an IC event, however more information would be required to make a definitive diagnosis.

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Patient ID	Study in Which AE of Interest Occurred	Treatment at the time of the Adverse Event	AE(s) of Interest Reported (Preferred Terms)	Additional Case information
0943012	MCP-103-305	Lin 290µg	Rectal hemorrhage	<p>This is a 36 year old female with a past medical history that included seasonal allergies, fatigue, migraines, and anxiety in addition to the chronic constipation. Concomitant medications included Mircette and Vitamin C. The patient was previously enrolled in trial MCP-103-303 and received Linaclotide 145mcg during the treatment period followed by placebo during the randomized withdrawal period. The patient experienced no adverse events during the double blind trial. She was rolled over into the open-label long-term trial and began taking Linaclotide 290mcg. On Trial day 365, the patient experienced mild rectal bleeding assessed as possibly related to study drug by the investigator. There was no action taken with regard to the study drug. The rectal bleeding persisted until trial day 398 (33 days) and eventually resolved without sequelae. In the opinion of this reviewer, this is possibly a case of ischemic colitis, however additional information would be required to make a definitive diagnosis.</p>

The sponsor's criteria for selection of cases of interest appear to be reasonable. However, patients may present with only diarrhea and rectal bleeding. Furthermore, in adjudicating the cases, for the likelihood of ischemic colitis, it is not entirely clear how one could assess the difference between a case having "Insufficient evidence to support the diagnosis of ischemic colitis" as opposed to a case of "Possible ischemic colitis". As previously stated the diagnosis of ischemic colitis requires a high index of suspicion. "Cases of interest" were chosen because the clinical presentation and information provided were consistent with "Possible ischemic colitis." These cases were to be examined to rule out ischemic colitis. Therefore it would seem more reasonable to assess each case for the probability of being a case of ischemic colitis rather than the possibility of a case being ischemic colitis. Given the transient nature of the disease, the variability of the clinical presentation, and in the absence of identifying an alternative cause for the symptoms, all "Cases of interest" could possibly be ischemic colitis until proven otherwise. It then would appear important to establish the probability of a case being related to the study product for each of the possible cases of interest. However, as previously stated a causal relationship between the study drug and development of the AE of interest may only be established by demonstrating a 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. This type of assessment would seem quite difficult to perform post-hoc and retrospectively. In the opinion of this reviewer, the applicant has shown due diligence in assessing for a possible relationship between their product and the development of ischemic colitis. Based on the evidence provided, there are a lack of data to suggest a causal association between the development of ischemic colitis and use of Linaclotide. It would be prudent, however, to continue close surveillance for the development of this issue in the post-marketing setting. Patients should also be warned of the signs and symptoms of ischemic colitis and advised to seek medical attention should they develop sudden onset of abdominal pain, diarrhea, and or rectal bleeding. Inclusion of this information in a MedGuide may also be advisable, but should not required given that a casual relationship between this product and the condition can not be established. The ischemic colitis issue may also addressed as a part of a class labeling for laxatives..

7.7.2 Diarrhea

Guanylate cyclase C is a key receptor responsible for acute secretory diarrhea. Linaclotide binds to and activates the guanylate cyclase c receptor increasing cyclic guanosine monophosphate (cGMP) both intracellularly and extracellularly. 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 fluid secretion and accelerated gastrointestinal transit.

During the clinical development of Linaclotide, diarrhea was the most frequently reported treatment emergent adverse event and the treatment emergent adverse event associated with the highest incidence of withdrawal. Because of this the applicant included a special analysis of diarrhea for patients in the double-blind trials. Specifically, the applicant presented:

- The time (days) from first dose of investigational product to the first occurrence of diarrhea by treatment group.
- The incidence of diarrhea-related TEAEs, SAEs, and early withdrawals for each treatment group by the time of first onset.
- The number and percentage of patients with a TEAE of diarrhea were presented according to their longest duration of diarrhea as categorized as follows: 1 day, 2 days, 3 to 7 days, 8 to 14 days, 15 to 28 days, > 28 days, and ongoing. (For this analysis patients were only counted once)
- The number and percentage of patients with a TEAE of diarrhea and shift in electrolytes by treatment group
- The number and percentage of patients with at least 1 episode of diarrhea who also experienced at least one other TEAE were summarized by SOC and preferred term.

The analysis of diarrhea was based on adverse event recordings as specified in each individual study protocol and assessment of patient reports to the Investigator. The applicant reported that there was no standardized definition for diarrhea, duration of diarrhea, or severity of diarrhea.

Because there was a lack of a standardized definition used to record episodes of diarrhea in the clinical trials of this drug development program, the incidence estimates reported may not adequately represent a “real world view” of what will be seen once the product becomes available to the wider general public. So, in the opinion of this reviewer, the results of the applicant’s analysis should be interpreted with caution. Diarrhea is a difficult condition to measure and there have been a number of different approaches used to measure diarrhea. The World Health Organization defines diarrhea as having three or more loose or liquid bowel movements per day.³⁹ There are also Rome criteria for chronic functional diarrhea. Much like constipation, there are a variety of subjective definitions of diarrhea based on, stool frequency, stool consistency, and duration of stooling. The variety of definitions has created a number of challenges to measuring diarrhea as an primary outcome and as an adverse event. For example, in epidemiological studies the challenges have included diagnosis based on self-reported symptoms; the variability of diarrhea in time, space and person; logistical burdens.⁴⁰

In the chronic idiopathic constipation population, 16% of patients taking Linaclotide 145µg/day and 14.2% of patients taking the Linaclotide 290µg/day developed at least 1 episode of diarrhea. Of those that took placebo, 4.7% developed diarrhea. None of the diarrhea TEAEs were reported as Serious Adverse Events. However, diarrhea was reported in one patient (0570150) who also experienced dehydration and orthostatic hypotension. (Please refer to section 5.3.2 for additional details.) Altogether, 1.8% (n = 15) of the patients receiving Linaclotide during the Treatment period of the double-blind CC trials developed severe diarrhea TEAEs and a total of 4.2% of Linaclotide patients discontinued from the Phase 3 placebo-controlled trials because of a TEAE of diarrhea. Most diarrhea TEAEs were mild to moderate in severity. A summary of the TEAEs of Diarrhea in patients with chronic idiopathic constipation is presented in the table below reproduced from the Applicant’s submission.

Table 98 Summary of Treatment-Emergent Adverse Events of Diarrhea in Chronic idiopathic constipation Patients in the Phase 3 Double-Blind Placebo Controlled Trials (Group 1) Safety Population.

<i>Preferred Term</i>	<i>Number (%) of Patients</i>			
	<i>Placebo (N = 423)</i>	<i>Linaclotide</i>		
		145 ug/day (N = 430)	290 ug/day (N = 422)	Linaclotide Total (N = 852)
Patients with at least 1 TEAE	222 (52.5)	262 (60.9)	235 (55.7)	497 (58.3)
Patients with Diarrhea TEAE	20 (4.7)	69 (16.0)	60 (14.2)	129 (15.1)
Diarrhea severity:				
Mild	10 (2.4)	26 (6.0)	21 (5.0)	47 (5.5)
Moderate	9 (2.1)	36 (8.4)	31 (7.3)	67 (7.9)
Severe	1 (0.2)	7 (1.6)	8 (1.9)	15 (1.8)
Discontinued due to diarrhea	2 (0.5)	20 (4.7)	16 (3.8)	36 (4.2)
SAE of diarrhea	0	0	0	0

Source: Table 8.6.2.1.1-1 Integrated Summary of Safety page 121.

More patients in the Linaclotide treatment groups experienced diarrhea as compared to the placebo groups. Of those patients with chronic idiopathic constipation who experienced a diarrhea TEAE, most experienced the diarrhea in the first two weeks of treatment and the events decreased over the 12 week treatment period. Of the 129 patients with chronic idiopathic constipation who experienced a diarrhea TEAE, 52.7% (n=68) experienced their first episode in the first week of treatment. The mean time from the first dose of double-blind treatment to the first TEAE of diarrhea was 16.4 ± 20.5 days for Linaclotide patients compared to 30.9 ± 29.1 days for the placebo patients. The median time to onset of the diarrhea TEAE was 6 days for the Linaclotide group and 17 days for the placebo group. The incidence of first occurrence of diarrhea by week is presented in the table below

Table 99 Incidence of Treatment Emergent Adverse Events of Diarrhea in CC Patients in the Phase 3 Double-Blind Placebo Controlled Trials (Group 1) by Time to Onset of first Occurrence

	Placebo (N = 423)		Linaclotide					
			145 ug/day (N = 430)		290 ug/day (N = 422)		Total (N = 852)	
	n (%) ^a	Cumulative n (%) ^b	n (%) ^a	Cumulative n (%) ^b	n (%) ^a	Cumulative n (%) ^b	n (%) ^a	Cumulative n (%) ^b
Patients with diarrhea TEAE	20 (4.7)	—	69 (16.0)	—	60 (14.2)	—	129 (15.1)	
Time of initial onset of diarrhea								
Day 1	0	0	16 (3.7)	16 (23.2)	13 (3.1)	13 (21.7)	29 (3.4)	29 (22.5)
Day 2	4 (0.9)	4 (20.0)	10 (2.3)	26 (37.7)	7 (1.7)	20 (33.3)	17 (2.0)	46 (35.7)
Days 3-7	0	4 (20.0)	10 (2.3)	36 (52.2)	12 (2.8)	32 (53.3)	22 (2.6)	68 (52.7)
Week 2	4 (0.9)	8 (40.0)	10 (2.3)	46 (66.7)	6 (1.4)	38 (63.3)	16 (1.9)	84 (65.1)
Week 3	3 (0.7)	11 (55.0)	5 (1.2)	51 (73.9)	3 (0.7)	41 (68.3)	8 (0.9)	92 (71.3)
Week 4	1 (0.2)	12 (60.0)	5 (1.2)	56 (81.2)	5 (1.2)	46 (76.7)	10 (1.2)	102 (79.1)
Week 5	1 (0.2)	13 (65.0)	0	56 (81.2)	6 (1.4)	52 (86.7)	6 (0.7)	108 (83.7)
Week 6	0	13 (65.0)	2 (0.5)	58 (84.1)	3 (0.7)	55 (91.7)	5 (0.6)	113 (87.6)
Week 7	1 (0.2)	14 (70.0)	2 (0.5)	60 (87.0)	0	55 (91.7)	2 (0.2)	115 (89.1)
Week 8	3 (0.7)	17 (85.0)	3 (0.7)	63 (91.3)	2 (0.5)	57 (95.0)	5 (0.6)	120 (93.0)
Week 9	0	17 (85.0)	1 (0.2)	64 (92.8)	2 (0.5)	59 (98.3)	3 (0.4)	123 (95.3)
Week 10	0	17 (85.0)	0	64 (92.8)	1 (0.2)	60 (100)	1 (0.1)	124 (96.1)
Week 11	1 (0.2)	18 (90.0)	3 (0.7)	67 (97.1)	0	60 (100)	3 (0.4)	127 (98.4)
Week 12 and later	2 (0.5)	20 (100)	2 (0.5)	69 (100)	0	60 (100)	2 (0.2)	129 (100)

Source: Table 8.6.2.1.2-1 Applicants Integrated Summary of Safety p. 123

a: For percentages within a given time period (Day 1, Day 2, Days 3-7, Week 2, etc.) the denominator is the safety population for that dose group.

b: For cumulative percentages, the denominator is the number of patients with a TEAE of diarrhea for that dose group.

The duration of diarrhea TEAEs varied in each treatment group and ranged from 1 day over 28 days. Interestingly the duration of diarrhea did not appear to be dose-related. Please refer to the table below. For those patients who were able to continue double-blind study drug treatment after experiencing a diarrhea TEAE, 75% (15/20) of placebo patients, 43% (30/69) of patients taking Linaclotide 145µg, and 47% (28/60) of patients taking Linaclotide 290µg, had their diarrhea resolve within 7 days.

Table 100 Duration of Diarrhea TEAEs in Chronic idiopathic constipation Patients in the Phase 3 Double-Blind Placebo Controlled Trials (Group 1) Safety Population.

Longest Duration of Diarrhea	Number (%) of Patients			
	Placebo (N = 423)	Linaclotide		
		145 ug/day (N = 430)	290 ug/day (N = 422)	Linaclotide Total (N = 852)
1 day	4 (0.9)	9 (2.1)	5 (1.2)	14 (1.6)
2 days	6 (1.4)	3 (0.7)	5 (1.2)	8 (0.9)
3-7 days	5 (1.2)	18 (4.2)	18 (4.3)	36 (4.2)
8-14 days	1 (0.2)	7 (1.6)	7 (1.7)	14 (1.6)
15-28 days	1 (0.2)	12 (2.8)	5 (1.2)	17 (2.0)
> 28 days	3 (0.7)	10 (2.3)	5 (1.2)	15 (1.8)
Ongoing	0	10 (2.3)	15 (3.6)	25 (2.9)
Total	20 (4.7)	69 (16.0)	60 (14.2)	129 (15.1)

Source: table 8.6.2.1.3-1 Applicant's Integrated Summary of Safety page 125.

For patients with multiple episodes of diarrhea, the episode with the longest duration is included in this table. For percentages, the denominator is the safety population for the dose group.

Because severe diarrhea can result in both dehydration and electrolyte shifts, special attention was given to these factors in the subgroup of patients who reported a diarrhea TEAE. In the chronic idiopathic constipation population of the double-blind placebo controlled trials (Group 1), 129 patients taking Linaclotide and 20 patients taking placebo had a diarrhea TEAE. Bicarbonate data were available for 127 of the Linaclotide patients. Of these, three (2.4%) had shifts in bicarbonate from normal to low. Of the 121 patients for whom potassium data were available, only 1 (0.8%) of 121 had a shift in potassium from normal to low; and 1 (0.8%) of 121 Linaclotide patients had a shift in potassium from normal to high. Over 98% of patients with chronic idiopathic constipation who reported at least 1 diarrhea TEAE in the combined Linaclotide treatment groups did not have a shift from baseline to end of treatment period in bicarbonate, chloride, magnesium, potassium, or sodium. Most patients had normal laboratory assessments at baseline and at the end of treatment. There were no appreciable differences noted between the 145µg and 290µg dose. None of the abnormal electrolyte values were potentially clinically significant.

Of the 129 Linaclotide treated patients who reported a diarrhea TEAE, 17 (13.2%) had a flatulence TEAEs {vs. 2 /20 (10%) placebo patients}, 13 (10.1%) had abdominal pain TEAEs {vs. 5/20 (25%) placebo patients}, 11 (8.5%) nausea TEAEs {vs. 4/20 (20%) placebo patients}, and 10 (7.8%) had abdominal distension TEAEs {vs. 2/20 (10%) placebo patients}, at some time during the study. Defecation urgency and fecal incontinence were each experienced by 6 (4.7%), dehydration by 4 (3.1%), and dizziness by 3 (2.3%) of the 129 Linaclotide treated patients with diarrhea TEAE compared with none of the 20 placebo patients who experienced diarrhea TEAE.

There were no TEAEs that might suggest volume depletion (e.g. dehydration, dizziness, orthostatic hypotension). TEAEs of interest occurring in patients who also experienced a diarrhea TEAE are presented in the table below.

Table 101 TEAEs of Interest in Patients with TEAEs of Diarrhea in Chronic idiopathic constipation Patients with Diarrhea TEAE in the Chronic idiopathic constipation Patients in the Phase 3 Double-Blind Placebo Controlled Trials (Group 1) Safety Population

Preferred Term	Number (%) of Patients			
	Placebo (N = 423)	Linaclotide		
		145 µg/day (N = 430)	290 µg/day (N = 422)	Linaclotide Total (N = 852)
Patients with at least 1 TEAE of diarrhea	20 (4.7)	69 (16.0)	60 (14.2)	129 (15.1)
Flatulence	2 (0.5)	9 (2.1)	8 (1.9)	17 (2.0)
Abdominal pain	5 (1.2)	6 (1.4)	7 (1.7)	13 (1.5)
Nausea	4 (0.9)	4 (0.9)	7 (1.7)	11 (1.3)
Abdominal distension	2 (0.5)	6 (1.4)	4 (0.9)	10 (1.2)
Defecation urgency	0	2 (0.5)	4 (0.9)	6 (0.7)
Fecal incontinence	0	4 (0.9)	2 (0.5)	6 (0.7)
Dehydration	0	1 (0.2)	3 (0.7)	4 (0.5)
Dizziness	0	0	3 (0.7)	3 (0.4)
Hematochezia	0	0	1 (0.2)	1 (0.1)
Orthostatic hypotension	0	0	1 (0.2)	1 (0.1)

Source: Applicant's Integrated Summary of Safety page 128. Note: TEAEs did not have to overlap the occurrence of diarrhea.

Assessments of intravascular volume depletion were also conducted. This was done to assess whether excess fluid loss via the GI tract might be occurring in patients who were experiencing diarrhea. In Group 1 patients, there were no patients on placebo who experience dehydration. Two (0.5%) of patients taking Linaclotide 145µg and 4 (0.9%) of patients taking Linaclotide 290µg experienced dehydration. In the patients with dehydration, a diarrhea TEAE was reported in 1 of the 2 patients receiving Linaclotide 145 µg and in 3 of the 4 patients receiving Linaclotide 290 µg.

Dizziness was reported by 2 (0.5%) of patients taking placebo, 4 (0.9%) of patients taking 145µg Linaclotide, and 6 (1.4%) of patients taking 290µg Linaclotide. In the patients with dizziness, diarrhea was reported as a TEAE in 0 of the 2 patients taking placebo, by 0 of 4 patients receiving Linaclotide 145 µg, and by 3 of the 6 patients receiving Linaclotide 290 µg. Orthostatic hypotension occurred in no patients on placebo, 1 (0.2%) of patients taking 145µg Linaclotide, and 2 (0.5%) of patients taking 290µg Linaclotide. In patients with orthostatic hypotension, diarrhea was reported as a TEAE in 1 of the 2 patients taking Linaclotide 290µg. Cases were reviewed were causality and did not appear to be directly related to diarrhea.

7.7.3 Gallbladder Disease

In the Phase 3 double-blind placebo controlled trials, 2 Linaclotide patients experienced cholelithiasis. There were 11 additional cases of cholelithiasis, 5 cases of gallbladder dyskinesia, and 2 cases of gallbladder cholesterolosis reported during the long-term safety trials. Altogether there were 20 cases of gallbladder disease in patients treated with Linaclotide. An OSE consult was solicited to determine if Linaclotide increased the risk of gallbladder disease. Please refer to the review of Dr. Carolyn McCloskey dated March 21, 2012 for additional information. In summary Linaclotide does not appear to increase the risk of gallbladder disease over the background rate of the U.S. population.

7.7.4 Aplastic Anemia

The reviewer previously noted that both trials patients in both Trials LIN-MD-01 and MCP-103-303 experienced noted potentially clinically significant lowering of the absolute lymphocyte count and absolute neutrophil count. One patient with chronic idiopathic constipation (patient #0563006 a 21 year old white male) was enrolled in the long-term safety trial after being found to be ineligible for trial MCP-103-303. Assessments of this patient's labs were remarkable for asymptomatic pancytopenia. The results of the patient's hematologic parameters are provided in the table below. Given the rare incidence of aplastic anemia, the applicant conducted a special assessment of Linaclotide post-hoc to assess for the drug's potential to induce pancytopenia.

Table 102 Hematologic Parameters for Chronic idiopathic constipation Patient #0563006 diagnosed with Aplastic Anemia

	February 11, 2009 Screening Visit	March 18, 2009 Day 1 of LTS Study (Drawn prior to Dosing)	June 24, 2009 Week 14 Visit	August 6, 2009
WBC x 10 ⁹ /L (WNL= 3.5 to 11.1 x10 ⁹ /L)	(b) (6)			
ANC x 10 ⁹ /L (WNL= 1.8 to 7 x10 ⁹ /L)				
Platelet count x 10 ⁹ /L (WNL=150 to 400 x10 ⁹ /L)				
Hemoglobin (g/L) (WNL= 132 to 170 g/L)				

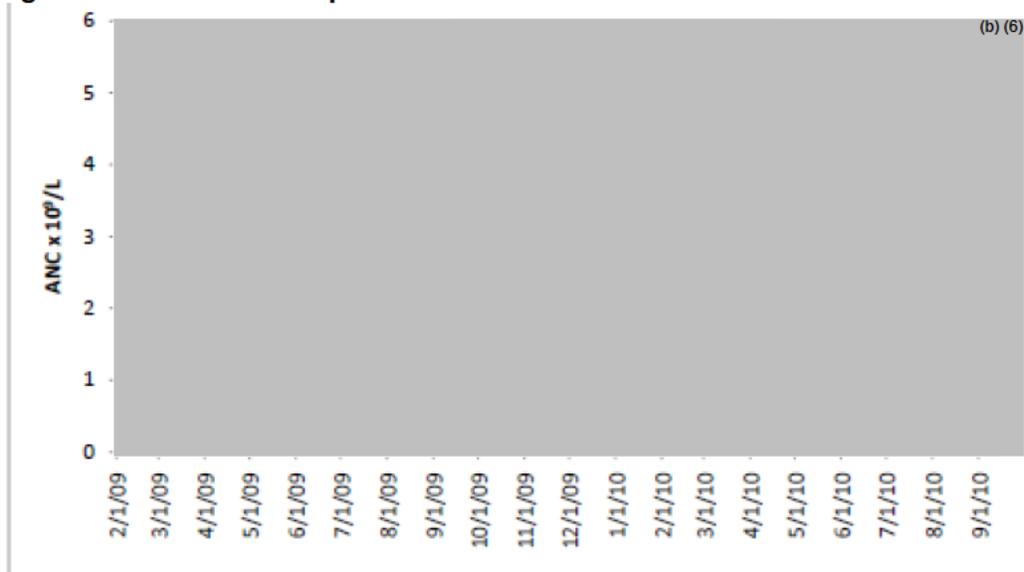
Source: Applicants Integrated Summary of Safety, Volume 2 page 2199-2235

WBC = White Blood Cells, WNL = within normal limits, ANC = Absolute Neutrophil Count.

No protocol- specified study site visits or lab evaluations were required between Day 1 and Week 14.

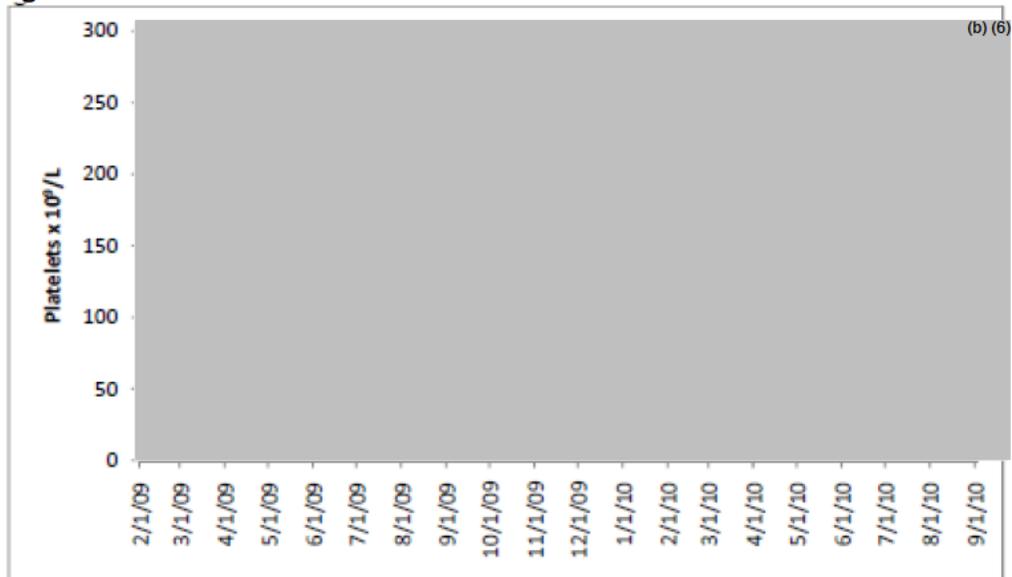
Patient had reportedly took study drug for approximately 3 months prior to cessation and being diagnosed and treated for aplastic anemia. The figure below details the changes in the patients absolute neutrophil, platelet, and hemoglobin over time.

Figure 20 Absolute Neutrophil Count over time Patient 0563006



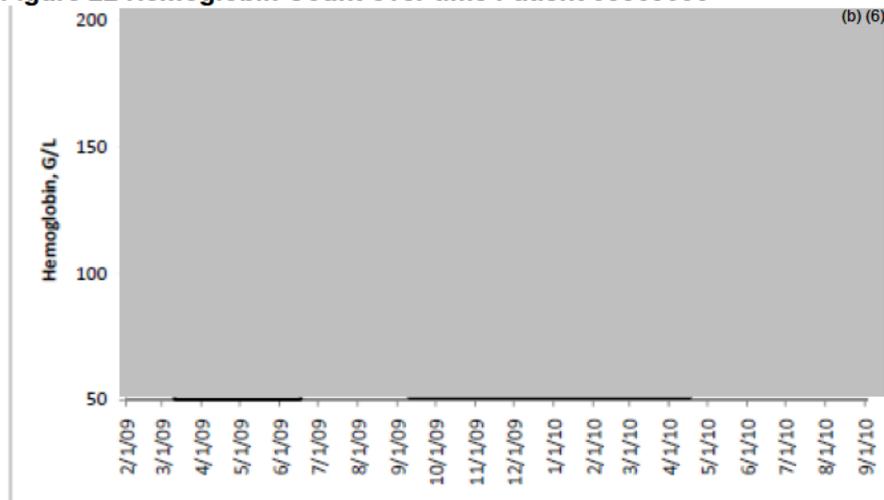
Source: Applicant's Integrated Summary of Safety page 2205

Figure 21 Platelet Count Over Time Patient 05363006



Source: Applicant's Integrated Summary of Safety page 2206

Figure 22 Hemoglobin Count over time Patient 05363006



Source: Applicant's Integrated Summary of Safety page 2206

The patient's past medical history was significant for recent "influenza" illness associated with diarrhea and seasonal allergies. He denied exposure to toxic chemicals or ionizing radiation. He was unemployed and worked odd jobs as a maintenance man. As a hobby he worked on cars on weekends and reported drinking 1 to 2 beers on weekends since age 18 years and smoking a half-pack of cigarettes a day since age 16 years. Family history was benign. Throughout his illness, the patient remained symptomatic. He was treated with transfusions and hematopoietic growth factors over several months before he was finally stabilized.

The applicant asserts that the decline in blood counts is consistent with a process than began prior to exposure to Linaclotide. Aplastic anemia is either inherited or acquired. Of the acquired cases, 50 to 65% are idiopathic.⁴¹ Most cases are not associated with drug or chemicals. To assess the association between Linaclotide and aplastic anemia, the applicant examine the safety populations of the Phase 3 trials and long-term safety studies. Exploratory analysis for trends in aberrations of the absolute neutrophil count, platelet count, and hemoglobin did not provide additional information regarding the effects of Linaclotide on blood cells. The incidence of potentially clinically significant values is presented in the Table below reproduced from the applicant's submission.

Figure 23 Incidence of Potentially Clinically Significant Values in ANC, Platelet Count, and Hemoglobin Double-Blind Placebo Controlled Phase 3 Trials

		Placebo N = 1218 n ^a /N ^b (%)					Linaclotide N = 1657 n ^a /N ^b (%)				
		Day 29	Day 85	Day 141	Day 183	Treat. Period	Day 29	Day 85	Day 141	Day 183	Treat. Period
ANC x 10 ⁹ /L	<0.8 × LLN	6/1143 (0.5)	6/1030 (0.6)	3/311 (1.0)	2/304 (0.7)	15/1180 (1.3)	17/1520 (1.1)	14/1335 (1.0)	3/297 (1.0)	4/289 (1.4)	30/1602 (1.9)
	>1.5 × ULN	3/1143 (0.3)	2/1030 (0.2)	0/311	2/304 (0.7)	7/1180 (0.6)	11/1520 (0.7)	5/1335 (0.4)	1/297 (0.3)	2/289 (0.7)	17/1602 (1.1)
Platelets x 10 ⁹ /L	<0.5 × LLN	0/1151	0/1035	0/311	1/303 (0.3)	1/1189 (0.1)	1/1519 (0.1)	0/1329	0/295	0/287	1/1608 (0.1)
	>1.5 × ULN	2/1151 (0.2)	1/1035 (0.1)	0/311	2/303 (0.7)	3/1189 (0.3)	0/1519	3/1329 (0.2)	0/295	0/287	3/1608 (0.2)
Hemoglobin (G/L)	<0.9 × LLN	9/1136 (0.8)	3/1024 (0.3)	1/306 (0.3)	1/299 (0.3)	15/1174 (1.3)	10/1522 (0.7)	6/1333 (0.5)	2/295 (0.7)	2/287 (0.7)	16/1605 (1.0)
	>1.1 × ULN	0/1136	0/1024	0/306	0/299	0/1174	0/1522	0/1333	0/295	0/287	1/1605 (0.1)

ANC = Absolute Neutrophil Count. ^aNumber of patients with a PCS value. ^bNumber of patients with a non-missing baseline value and at least one non-missing value at the scheduled visit.

Source: Applicants Table 8 Integrated Summary of Safety Volume 2, page 2221.

According to the applicant, Linaclotide is unlikely to be an etiologic agent for aplastic anemia. In 26-week mice and 39-week monkey toxicology studies, Linaclotide doses of up to 4,000-fold the therapeutic dose did not produce evidence of myelosuppression, based on examination of peripheral blood cell counts and bone marrow histology. The applicant further asserts that based on Linaclotide's peptide structure and pharmacologic properties, as well as the absence of significant hematologic findings in the clinical trial database, Linaclotide is unlikely to cause aplastic anemia. The applicant also argues that the clinical presentation of patient #0563006, particularly the marked drop in blood counts prior to Linaclotide treatment, suggests that the disease process culminating in aplastic anemia began prior to Linaclotide exposure, and is most likely idiopathic. This reviewer agrees with the applicant's assessment. However, given the changes in hematological parameters noted in Section 5 of this review, additional surveillance may be warranted in the post-market setting.

8 Postmarket Experience

Linaclotide is not marketed anywhere in the world. Therefore there is no post-marketing data available.

9 Appendices

9.1 Advisory Committee Meeting

There was no Advisory Committee meeting for this NDA application.

9.2 Events of Presubmission Regulatory History

Date	Summary of Events
August 4, 2004	<p>Type B meeting to discuss the use of MD-1100 acetate for the treatment of constipation predominant irritable bowel syndrome (IBS-C), (b) (4) and chronic idiopathic constipation (CC). In lieu of a face to face meeting, the sponsor accepted written responses send on July 14, 2004. Agency stated that evaluation of the adequacy of characterization of test material will occur when IND is submitted. Agency agreed with sponsor's approach for conducting general toxicology studies. The sponsor stated that they had conducted two GLP genetic toxicology studies, an Ames assay for mutagenesis, and a chromosomal aberrations assay for clastogenicity. The Agency agreed that no further genotoxicity studies were required. Agency also agreed that no neurobehavioral toxicology studies beyond obtaining clinical observations from general toxicology studies were required. Sponsor stated they would conduct chronic safety studies in rodent and nonrodent species. However they did not intend to perform traditional carcinogenicity studies. The Agency stated that results of subacute toxicity studies and future subchronic toxicity studies would need to be assessed before agreeing that carcinogenicity studies would not be required. Sponsor stated their intent to use surrogate pharmacodynamic endpoints in Phase II dose-ranging studies. Agency stated that in addition to PK studies, quantitative fecal and urinary recovery of the study drug and metabolites must be demonstrated in a mass balance study. A colonic transit test using radio-opaque markers was recommended to assess the drug's pharmacodynamic effects. Agency stated that a single ascending dose safety study must be performed and assessed before multi-dose studies could commence. Agency recommended that the multiple dose study be conducted in normal healthy volunteers first.</p>
September 30, 2004	<p>IND 63290 was submitted by Microbia, Inc. for a Phase 1 study to be conducted with MD-1100 Acetate for the treatment of IBS C. Study is deemed safe to proceed. Doses studied were 30µg, 100µg, 300µg, 1000µg, and 3000µg among 5 separate cohorts.</p>
November 9, 2004	<p>Advice letter to sponsor—Obtain 12 lead ECG at 24 and 48 hours post dose to fully evaluate any potential drug-associated ECG effects. Conduct a quantitative fecal and urinary recovery of the drug and metabolites in a mass balance study.</p>
May 5, 2005	<p>Teleconference with sponsor to discuss amendments to Protocol MCP-103-002 entitled "Clinical Protocol for a Seven Day, Oral Multiple Ascending Dose, Placebo-Controlled Study of MD-1100 in Healthy Subjects". The amendment proposed language be added to the protocol to clarify that changes in bowel habits should not be considered adverse events since such changes are expected pharmacodynamic effects of MD-1100 Acetate and are collected on Bristol Stool forms. The Agency requested that the sponsor rescind their proposal due to safety concerns and maintained that a pronounced pharmacological effect may also be treated as an adverse event, based on pre-specified definitions of diarrhea and constipation. Division recommended sponsor use definitions outlined in Rome criteria for diarrhea and constipation. Sponsor agreed.</p>
October 20, 2005	<p>Type C Industry Meeting with Sponsor. Sponsor stated that analysis of the data from the Phase 1 study revealed that some study participants met criteria for both constipation and diarrhea currently (based on previously proposed prospective definitions of the conditions). The sponsor proposed that in future clinical studies where subjects will be entering the clinical studies with constipation at baseline, they</p>

Date	Summary of Events
	<p>rely on patient reporting of an exacerbation of their symptoms for identification of constipation adverse events and rely on patient reporting of diarrhea for recording diarrhea adverse events. Sponsor also proposed to independently capture occurrences of exacerbations of constipation and diarrhea using a revised approach to capturing the information. Agency agreed. Agency also made recommendations for the primary endpoint to be used in Phase 3 trials of IBS-C and CC. For efficacy assessment in the treatment of IBS, Agency recommended that the patients global assessment of symptoms and clinically meaningful change in a validated IBS symptom severity scale be used as co-primary endpoints. Agency suggested efficacy assessments after 8 to 12 weeks of treatment for IBS-C. Agency stated that proposed Phase 2 studies should follow patients for 4 weeks after 12 week treatment phase during which withdrawal effect and safety assessments could be evaluated. Agency stated that assessments of behavioral and psychological disorders is important in the evaluation of patients with IBS and should be included in the outcome analysis. Definitions of responders and non-responders should be specified prospectively. The nonclinical reviewer pointed out that despite minimal drug absorption, signs of systemic toxicity occurred in the 14-day oral toxicity study in monkeys (i.e. increased AST & ALT levels and kidney lesions. At this time, there was insufficient information to determine if carcinogenicity studies were needed. The issue could not be resolved until the subchronic (90 day) and chronic toxicology studies were submitted. Dose selection for general toxicology studies should be based on results from completed toxicology studies so that target organ toxicity could be identified. Agency also provided guidance on dose selection for reproductive toxicology studies. CMC advice provided for characterization of the drug substance and need to demonstrate the impurity profile. Agency agreed that sponsor may rely on <i>in vitro</i> dissolution testing.</p>
February 13, 2006	<p>Sponsor had previously sent correspondence to the Agency regarding acceptable clinical endpoints for chronic idiopathic constipation studies. Advice letter sent to sponsor suggesting the sponsor request a meeting and submit a draft protocol with specific questions to discuss. Agency also recommended that in defining clinical responders and endpoints in clinical trials for chronic idiopathic constipation, the proposed primary and secondary endpoints should include the effects of MD-1100 on all aspects of Rome criteria for the condition.</p>
June 5, 2006	<p>Teleconference between Microbia and the Division of Gastroenterology Products. Sponsor stated that their primary endpoint for both Phase 2 and 3 trials is the difference in the mean change from Pre-Treatment Period to Treatment Period in the frequency of spontaneous bowel movements. The sponsor also stated that the secondary endpoints will reflect the other criteria for chronic idiopathic constipation in Rome II and include change in degree of straining, stool consistency, and sensation of complete evacuation. The Division recommended that the protocol define a responder based on a clinically meaningful endpoint (e.g. ≥ 3 spontaneous bowel movements (SBM) or complete spontaneous bowel movements (CSBM) per week <u>and</u> an increase of at least one SBM or CSBM per week compared to baseline. Agency recommended that the primary efficacy analysis be revised to a response rate during each week of the entire treatment period. Agency recommended that the sponsor expand their overall efficacy and safety databases to include safety and efficacy data in a heterogeneous population of subjects; extend the treatment period in Phase 3 trials to at least 12 weeks duration followed by a 4-week withdrawal period; and expand the overall long-term safety database. Agency also suggested possible secondary</p>

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	<p>endpoints. Agency also recommended that the sponsor expand the overall long-term safety database to 1 year of exposure. Because, of its limited systemic exposure, the sponsor stated that they did not intend to conduct traditional ADME, special population, and pharmacokinetic studies. Agency requested studies to verify that there is a lack of systemic bioavailability of the product. If data are adequate, the sponsor's proposal to not conduct traditional pharmacokinetic studies may be acceptable. Agency also requested additional toxicology studies. If there is systemic absorption, the Agency stated. Sponsor proposed to use the "Patient Assessment of Constipation Quality of Life, PAC-QOL" in lieu of the previously proposed IBS-QOL. The Agency agreed to review the proposal after submission. Discussion regarding the justification of the time interval chosen for rescue medication. Agency reiterated that sponsor will need to perform QTc studies if there is systemic absorption of the drug.</p>
June 12, 2006	<p>Advice letter providing detailed instructions related to toxicology study requirements.</p>
September 25, 2006	<p>Meeting with Sponsor to discuss primary and secondary endpoints for IBS-C clinical trials as well as the overall clinical development program. Agency agreed that pooling data from the long-term safety trials was appropriate.</p>
January 11, 2007	<p>Meeting between the Sponsor and the Agency to discuss the necessity for human and animal mass balance studies, carcinogenicity studies, and the use of an absolute dose for the planned chronic toxicology studies. Agency agreed that the sponsor did not have to conduct nonclinical mass balance or biotransformation studies. Agency stated that doses in the chronic toxicity studies in rats and monkeys should not be less than those used for the 13 week toxicity studies in those species. Additional comments reserved pending further data review. Sponsor is required to conduct carcinogenicity studies. Human and nonclinical mass balance studies are not required. Agency suggested that Microbia conduct a nonclinical study to observe renal clearance of the drug. THERE were renal changes in the 13-week toxicology study in monkeys at high dose. Agency also recommended that Microbia assess brain, liver, and adipose tissue for any accumulation of Linaclotide following more chronic dosing. Agency stated that given the available data, they could not agree that Linaclotide cannot be detected inhuman plasma nor could they agree with sponsor's proposal not to conduct further PK and TQTc studies in humans. Agency recommended that Microbia document and justify why they can not measure PK in order to assess DDI and exposure in lactating women.</p>
February 15, 2007	<p>Advice letter to sponsor from nonclinical. Additional nonclinical study reports are needed for review prior to the initiation of the Phase 3 trials.</p>
February 22, 2007	<p>Advice letter to sponsor regarding nonclinical issues.</p>
April 6, 2007	<p>SEALD review states that primary endpoint for clinical trials is not acceptable and recommends revisions.</p>
April 9, 2007	<p>Sponsor requests SPA agreement for nonclinical carcinogenicity studies.</p>
April 19, 2007	<p>Type B Meeting between the sponsor and Agency to discuss primary endpoint used in IBS-C phase 2b and 3 clinical trials, duration of treatment and administrative issues. Agency stated that to obtain a claim for long-term use of the drug, the trial duration need to be 6 to 12 months. Trials should include a 4 week post-treatment period in order to assess for rebound constipation. Full nonclinical study reports needed to support the Phase 3 studies will be submitted no later than one month prior to the initiation of Phase 3.</p>

Date	Summary of Events
April 14, 2008	Sponsorship of IND 63,290 changed from Microbia to Ironwood Pharmaceuticals
May 7, 2008	SEALD Review of primary endpoint for Chronic idiopathic constipation trials. The primary efficacy endpoint will be complete spontaneous bowel movement overall responders for 9 out of the 12 weeks of the trial. Agency recommends that the definition also include a patient rating of change question which quantifies the patient's assessment of improvement. Agency recommends that the sponsor consider developing/utilizing an instrument which, based upon patient input represents a meaningful, complete, comprehensive, and appropriate measure of constipation. Additional justification required for the proposed secondary endpoints.
May 15, 2008	<p>End of Phase 2 meeting held. Sponsor seeking agreement concerning the Phase 3 trials, the impact of the renal clearance rate data, and pediatric deferral. Separate End of Phase 2 meeting held for IBS-C indication. Agency agrees that drug-drug interaction studies are not needed because Linaclotide is not quantifiable in human plasma at the anticipated therapeutic doses and the potential of Linaclotide to affect the GI absorption of drugs such as digoxin can be addressed through labeling. Agency stated that the sponsor would not need to conduct a TQTc study to help characterize the effect of the drug on cardiac conduction. Preclinical studies in animals have shown systemic effects and therefore there is a potential for systemic effects in humans. The details of the potential systemic bioavailability of Linaclotide and/or its resulting metabolites are still under investigation. The TQTc study may be carried out in parallel with the clinical trials. Agency stated that in light of the significant formulation changes, the sponsor would need to conduct Phase 3 trials with the to-be-marketed formulation. Sponsor's will discuss formulation changes during a forthcoming CMC meeting. Agency stated that it was acceptable for sponsor to enroll patients in the Phase 3 clinical trials using Rome II criteria rather than Rome III criteria. Agency agreed to Phase 3 trial inclusion and exclusion enrollment criteria. Agency reiterated that the definition of responder (for the primary endpoint) should include a clinically meaningful change for the patient. Agency also stated that the sponsor has not justified that the proposed secondary endpoints (b) (4).</p> <p>. Agency stated that if results for the subpopulation of patients >65 years old are similar to those obtained in the general population, they might support an indication that includes the >65 years of age group. However, the results would be considered exploratory if the study was not designed to demonstrate efficacy in the specific sub-groups. Agency agreed with the proposed 300 µg dose. Both phase 3 trials for CIC are required to have a randomized withdrawal phase. Agency agreed that patients ineligible for randomization into the Phase 3 trials could be enrolled into the long-term safety study. Agency agreed that combining the long-term safety databases for the CIC and IBS-C indications was acceptable. Deferral of pediatric trials under PREA discussed. Sponsor noted its intention to submit information about its pediatric development plan in the End of Phase 2 meeting background package for IBS-C.</p>
August 7, 2008	Type B End of Phase 2 meeting to discuss the Phase 2 program for IBS-C.
September 3, 2008	Advice Letter to the sponsor stating that a TQT study is not need for Linaclotide. It appears that at therapeutic doses, Linaclotide and its metabolite have not been detected in the plasma. At supra-therapeutic doses, Linaclotide was detected at the highest concentration in 2 of 18 subjects but none of the metabolite was detected. Agency recommends that ECGs be collected in Phase 3 clinical trials. Patient with elevated OTC at baseline should be excluded from the Phase 3 clinical trials.

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	Additional elements with regard to ECG acquisition and interpretation were stipulated.
October 14, 2008	Type A meeting. Additional discussions between Agency and Sponsor regarding the IBS-C endpoints.
November 6, 2008 -	End of Phase 2 Chemistry Manufacturing and Controls (CMC) meeting held. (Meeting minutes revised June 01, 2009)
April 4, 2009	Nonclinical Advice letter.
November 17, 2008	Letter Correspondence between Agency and Sponsor
January 26, 2010	IND 63,290 Type C meeting to discuss the adequacy of the proposed pediatric plan for Linaclotide. [Pediatric Maternal Health Staff and Patient-Reported Outcome (PRO) Team consulted] Pediatric dosing trials may not commence until after the NDA review of safety
May 20, 2010	CMC meeting to discuss the Development of Linaclotide
May 20, 2010	Advise letter to the sponsor stating that at least 4 complete IVRS calls per week are necessary for inclusion in the weekly responder analysis, otherwise patients will be considered nonresponders. Agency recommends that sponsor retains the original prespecified definition of a weekly CSBM responder. If the definition is changed prior to database lock, than the clinical meaningfulness will be a review issue. If the definition of an overall responder is changed, than sponsor should analyze data using both the original overall responder definition and the revised definition.
January 20, 2011-	IND 63,290 Type C meeting to reach agreement on CMC development program. In lieu of quantifying peptide content applicant proposed to quantify Linaclotide content. Agency accepted applicants "gravimetric approach" for qualifying the Linaclotide reference standard. However the acceptability of methods for determining additional variables would be subject to NDA review. Agency agreed that adequate data were provided to establish the identity of Linaclotide degradation products. The Agency also noted that a final determination of the qualification threshold for these degradants would be based on review of full study reports. New safety concerns identified during the review may result in a need to lower the limits of the degradants. Additional studies may be required. The sponsor was asked to explain the source of the (b) (4) that reacts with the drug substance. The Agency also agreed with how dose adjustments would be captured from nonclinical studies and clinical trials completed prior to the change in method of qualifying the Linaclotide reference standard. The sponsor's approach to revising the proposed commercial drug product dose was found to be reasonable. The sponsor will provide detailed information about the conversion factor used to arrive at the commercial dose when the NDA is submitted.
March 22, 2011	Type B Pre-NDA Meeting Clinical pharmacology recommends sponsor studies the effects of Linaclotide and the metabolite on induction of CYP enzymes. Sponsor states that given the low systemic exposures following therapeutic doses, induction of CYP enzyme is unlikely. Sponsor will evaluate requirements for in vitro induction studies. There appears to be adequate clinical trial data for NDA filing. Sponsor will provide separate Summaries of Clinical Efficacy for each indication. Sponsor will provide one summary of Clinical Safety for both indications. Clinical studies will be organized into groups based on study phase, study design, and subject population. Sponsor will provide integrated safety analysis for all Linaclotide treated patients in the pivotal and long-term safety trials. There are 25 duplicate patients in the clinical trials dataset. Agreement reached regarding the

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	sensitivity analyses for these patients. Sponsor will submit all PD results for review. Agency agreed to accept a summary listing of patients who experienced SAEs (instead of CRFs and narratives) for those SAEs reported after the data cut-off date of October 11, 2010. A final decision regarding the need for an Advisory Committee is pending. The proposed pediatric plan may be reasonable. A validated PRO is needed for pediatric patients.
May 11, 2011	Pre-NDA CMC Meeting scheduled for this time was cancelled. Sponsor accepted preliminary comments dated May 4, 2011. Sponsor encouraged to continue to collect data to determine if the routine manufacturing and testing programs produce consistently acceptable product lots. Manufacturers overall stability plan is acceptable. The planned structure and organization of the quality sections are acceptable

Reviewer's Table

9.3 Bristol Stool Chart

Bristol Stool Chart

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

9.4 7 Point Ease of Passage Scale

- 1 = Manual disimpaction/enema needed
- 2 = Severe straining
- 3 = Moderate straining
- 4 = Mild straining
- 5 = No straining
- 6 = Urgency
- 7 = Incontinent

9.5 Criteria for Potentially Clinically Significant Laboratory Test Results

<i>Parameter</i>	<i>SI</i>	<i>Low Limit</i>	<i>High Limit</i>
CHEMISTRY			
Albumin	g/L	< 0.9 × LLN	> 1.1 × ULN
Alanine aminotransferase	U/L	—	≥ 3 × ULN
Alkaline Phosphatase	U/L	—	≥ 3 × ULN
Aspartate aminotransferase	U/L	—	≥ 3 × ULN
Bicarbonate	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Bilirubin, total	umol/L	—	> 1.5 × ULN
Calcium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Chloride	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Cholesterol	mmol/L	—	> 1.6 × ULN
Creatinine	umol/L	—	> 1.3 × ULN
Glucose, nonfasting	mmol/L	< 0.8 × LLN	> 1.4 × ULN
Magnesium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Phosphate	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Potassium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Sodium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Total protein	g/dL	< 0.9 × LLN	> 1.1 × ULN
Urea (blood urea nitrogen)	mmol/dL	—	> 1.2 × ULN
Uric acid	mg/dL	< 0.9 × LLN	> 1.1 × ULN
HEMATOLOGY			
Basophils absolute cell count	10 ⁹ /L	—	> 3 × ULN
Eosinophils absolute cell count	10 ⁹ /L	—	> 3 × ULN
Hematocrit	Rati	< 0.9 × LLN	> 1.1 × ULN
Hemoglobin	g/L	< 0.9 × LLN	> 1.1 × ULN
Lymphocytes absolute cell count	10 ⁹ /L	< 0.8 × LLN	> 1.5 × ULN
MCH	P	—	> 3 × ULN
MCHC	G/L	—	> 3 × ULN
MCV	fL	< 0.9 × LLN	> 1.1 × ULN
Monocytes absolute cell count	10 ⁹ /L	—	> 3 × ULN
Neutrophils absolute cell count	10 ⁹ /L	< 0.8 × LLN	> 1.5 × ULN
Platelet count	10 ⁹ /L	< 0.5 × LLN	> 1.5 × ULN
Red blood cell count	10 ¹² /L	< 0.9 × LLN	> 1.1 × ULN
White blood cell count	10 ⁹ /L	< 0.7 × LLN	> 1.5 × ULN
URINALYSIS			
pH	—	< 0.9 × LLN	> 1.1 × ULN
Specific gravity	—	—	> 1.1 × ULN

LLN = lower limit of normal value provided by the laboratory; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; ULN = upper limit of normal value provided by the laboratory

Source: Table 4.3.10.1-1 Applicant's submission, Integrated Summary of Safety p. 41.

9.6 Potentially Clinically Significant Vital Signs

Vital Sign Parameter	Flag	Criteria*	
		Observed Value	Change from Baseline
Systolic Blood Pressure (SBP) (mmHg)	High	≥ 180	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Diastolic Blood Pressure (DBP) (mmHg)	High	≥ 105	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Pulse Rate (beats per minute)	High	≥ 120	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Weight (kg)	High	—	Increase of ≥ 7 %
	Low	—	Decrease of ≥ 7 %

*A postbaseline value was considered a PCS value if it met both criteria for observed value and change from baseline
 Source: Table 4.3.10.2-1 Applicants Submission Integrated Summary of Safety p. 42

9.7 Potentially Clinically Significant ECG Parameters

ECG Parameter (msec)	Upper
QRS interval	≥ 150
PR interval	≥ 250
QTc interval	> 500
Change from baseline in QTc	≥ 60

Note: QTc PCS criteria apply to both QTcB (Bazett) and QTcF (Fridericia (Fridericia) ECG = electrocardiogram; QTc = QT interval corrected for heart rate.

Source: Table 4.3.10.3-1 Applicant's Integrated Summary of Safety p. 43.

9.8 Sample Adjudication Form for Assessment of Ischemic Colitis. Evaluation Form

Part A: Criteria for Identification of Cases

Please complete the following questions (check the appropriate box):

Question	Yes	No
1. Did the patient have abdominal pain reported as an adverse event?		
2. Did the patient have an adverse event consistent with lower GI bleeding?		
3. Did the start date of the adverse events of abdominal pain and lower GI bleeding occur within 3 days of each other (note that either event may have occurred first)?		

Part B: Assignment of Category

1. Based on your clinical judgment, choose the box next to the category that best fits the patient's history, clinical course, and results of any evaluations that might have been performed. (Place an "X" by the appropriate category.)

Category	Choose Category "X"
A. Insufficient evidence to support the diagnosis of ischemic colitis	
B. Possible ischemic colitis - The diagnosis is supported primarily by clinical evidence. - Some cases include radiographic and/or endoscopic findings that were compatible with, but not diagnostic of, ischemic colitis.	
C. Probable ischemic colitis - The diagnosis is supported by clinical evidence PLUS - Endoscopic and/or biopsy findings. - In some cases with good documentation of biopsy and/or endoscopy findings, but poor documentation of clinical evidence, the clinical evidence was assumed.	

2. In the space below, provide your rationale for the category that you chose in the previous question.

3. In the space below, provide your impression of the most likely etiology of the patient's symptoms.

Part C: Relatedness to Treatment

(to be answered only if you provided a response of "possible" or "probable" ischemic colitis in Part B)

1. Choose the box next to the category that best describes the relationship of study drug to ischemic colitis. Details regarding the particular categories is provided on Page 3. (Place an "X" by the appropriate category.)

Category	Choose Category "X"
Definitely Related	
Probably Related	
Possibly Related	
Probably Not Related	
Definitely Not Related	

Categories of Association between Study Drug and an Adverse Event

Definitely Related

- Exposure & Sequence is correct. Symptoms develop after patient starts medication; adverse event diagnosed after patient starts medication; patient on medication long enough for adverse event to be related to medication use; adverse event diagnosed during medication use or shortly after discontinuation of medication.
- Positive de-challenge: symptoms of adverse event resolve with withdrawal of medication
- Positive re-challenge: symptoms of adverse event return with re-institution of medication
- No obvious competing cause that led to adverse event
- Objective evidence to support the diagnosis of an adverse event

Probably Related

- Exposure & Sequence is correct.
- Positive de-challenge
- No Re-challenge
- No obvious competing cause that led to adverse event
- Objective evidence to support the diagnosis of an adverse event

Possibly Related

- Exposure & Sequence is correct.
- De-challenge ambiguous or negative
- No re-challenge
- No obvious competing cause that led to adverse event
- Objective evidence to support the diagnosis of an adverse event

Probably Not Related

- Exposure & Sequence partly correct.
- Competing cause(s) are more likely cause of adverse event
- Ambiguous or conflicting evidence to support the diagnosis of an adverse event
- De-challenge ambiguous or negative
- No Re-challenge

Definitely Not Related

- Exposure & Sequence mostly incorrect: symptoms of adverse event develop before patient starts medication; adverse event diagnosed long after patient stops medication; adverse event diagnosed before patient starts medication.
- Competing cause(s) are more likely cause of adverse event.
- Ambiguous or conflicting evidence to support the diagnosis of adverse event.
- De-challenge ambiguous or negative
- No re-challenge

An adverse event case does not need to fulfill all criteria in a specific category in order to be classified in that category.

The criteria in each category are *guides* to determine if an adverse event was definitely related, probably related, possibly related, probably not related, or definitely not related to medication use. You should utilize your judgment and clinical expertise to assess the data from a case and decide if use of medication use was associated with the adverse event case.

2. In the space below, provide your rationale for the category that you chose in the previous question.

9.9 Labeling Recommendations

All labeling recommendations are subject to formal negotiations with the applicant. The available labeling at the time of this review is provided in the Appendix. The following table reflects the clinical reviewer's labeling suggestions. *Reviewer's Comments are in Italics.*

<u>Applicant's Proposed Labeling Section</u>	<u>Suggested Labeling Revisions and Language</u>
<u>HIGHLIGHTS OF PRESCRIBING INFORMATION</u>	<u>HIGHLIGHTS OF PRESCRIBING INFORMATION</u>

(b) (4)



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/s/

ERICA WYNN
08/01/2012

ROBERT FIORENTINO
08/02/2012

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202-811
Priority or Standard	Standard
Submit Date(s)	8/8/2011
Received Date(s)	8/8/2011
PDUFA Goal Date	6/8/2011
Division	Gastroenterology and Inborn Errors Products (DGIEP)
Reviewer Name(s)	Lara Dimick-Santos, MD, FACS
Review Completion Date	4/12/2012
Established Name (Proposed) Trade Name	Linacotide LINZESS®
Therapeutic Class	Guanylate Cyclase C (GC-C) Receptor Agonist (First in Class)
Applicant	Forest Laboratories, Inc. Ironwood pharmaceuticals, Inc.
Formulation(s)	Capsule
Dosing Regimen	290µg one time daily
Indication(s)	Treatment of Irritable Bowel Syndrome with Constipation
Intended Population(s)	Patients ≥ 18 years of age

Template Version: [March 6, 2009](#)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The risk-benefit balance is in favor of an approval action for linaclotide for the indication of treatment of Irritable Bowel Syndrome with Constipation in adults. Final labeling changes are in process as of the date of this review. The labeling will carry a boxed warning with a contraindication for use of linaclotide in pediatric patients' up to 6 years of age and a warning against use in pediatric patients' 6 through 16 years of age, until such time that further information is obtained. Final approval is contingent upon the applicant incorporating the Food and Drug Administration's recommended changes to the drug label and adhering to the required Phase IV commitment studies.

1.2 Risk Benefit Assessment

Linaclotide is a small peptide that is intended for the treatment of adult patients with Irritable Bowel Syndrome with Constipation (IBS-C) and Chronic Idiopathic Constipation (CIC). This summary will address the safety and efficacy for the IBS-C indication; however, safety review includes data from both indications.

There is a significant unmet medical need for patients with IBS-C because it affects a large population, about 2% of the US population, with significant symptoms. It is a public health concern secondary to the significant loss in productivity, and the serious, disabling symptoms in a small subset of patients. There is only one other approved agent on the market (lubiprostone), and it is labeled as restricted to use in women. Zelnorm, which was withdrawn from the market, is restricted to Emergency IND applications secondary to cardiovascular risks. The alternative therapies available are only minimally to moderately effective. See discussion under Section 2.6 Other Relevant Background Information on page 21.

Linaclotide showed clinical benefit in decreasing abdominal pain and improving stool consistency in patients with IBS-C. Two well designed, large placebo-controlled trials provided evidence of efficacy of the 290µg dose over placebo. Linaclotide has very low systemic exposure and no known drug/drug interactions. The applicant did not perform phase 3 efficacy trials with the lower dose (145 µg) of linaclotide that was used in CIC patients and in the long-term safety trials. Exploration of the lower dose would have been ideal. See discussion in Efficacy Summary in Section 6 Review of Efficacy on page 93.

The safety profile of linaclotide is generally favorable, with adverse events (AEs) occurring primarily in the gastrointestinal tract. Diarrhea is the most common AE, occurring in approximately 17% of treated patients in the placebo-controlled trials, and in more than 30% of patients in the long-term trials. There

is not a clear dose response for diarrhea AEs in the two doses tested in the CIC controlled trials; however, dose reduction from 290µg to 145µg occurred in 32% of patients in the long term trials, mostly for diarrhea. Serious GI AEs were rare. However, severe diarrhea occurred in 2% of patients. Diarrhea and other GI AEs generally occurred in the first few weeks of treatment. Labeling should reflect the risk of diarrhea. The labeling will carry a boxed warning with a contraindication for use in pediatric patients' up to age 6 years and a warning to avoid use in pediatric patients' 6 through 16 years of age, secondary to the preclinical data showing deaths in very young mice. There were no other safety signals identified, though an evaluation for ischemic colitis and other GI events were performed. See discussion in Safety Summary in Section 7 Review of Safety – IBS-C and CIC - Combined Indications on page 115 and Section 2.5.2 Pediatric Information on page 16.

The risk-benefit balance is in favor of approval of linaclotide for the IBS-C indication in adults, with labeling changes. The safety profile is good, with diarrhea being the most common adverse event. Alleviating an unmet medical need for IBS-C patients should be achieved with the approval of linaclotide. Post-marketing surveillance should monitor for events of serious diarrhea, dehydration, hypotension and ischemic colitis. Linaclotide will be contraindicated in pediatric patients up to age 6 and carry a warning to avoid use in pediatric patients' age 6 through age 16 years of age.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Post-marketing surveillance for events of serious diarrhea, orthostatic hypotension, dehydration or ischemic colitis should be preformed. While these events were rare in the clinical data sets, the seriousness of these events warrents monitoring.

1.4 Recommendations for Postmarket Requirements and Commitments

No clinical PMC's or PMR's are recommended at this time. (b) (4)

(b) (4) in light of preclinical data showing a large number of deaths in infant mice; the clinical trials in pediatrics will be continued to be deferred until further data on the mechanism of the deaths in mice the relevance to humans can be obtained and reviewed. The sponsor may proceed with development of age specific PRO instruments for evaluation of IBS-C in children. The sponsor has indicated that they will submit a revised PPSR with a protocol for the planned mice study, which has been discussed with the sponsor during a t-con.

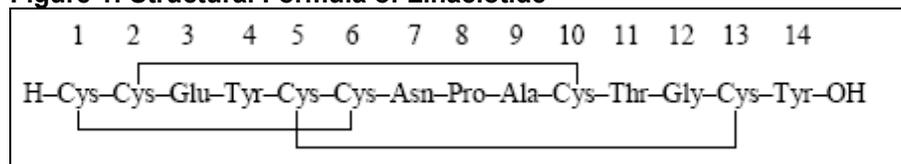
2 Introduction and Regulatory Background

2.1 Product Information

Linaclotide is an orally administered therapeutic agent developed for the treatment of chronic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C). Linaclotide is a chemically synthesized 14-amino acid peptide with 3 disulfide bonds.

The drug product is supplied as hard gelatin capsules in 145 ug and 290 ug strengths.

Figure 1: Structural Formula of Linaclotide



Linaclotide is a first-in-class guanylate cyclase C (GC-C) receptor agonist, structurally related to the endogenous guanylin peptide family. In the gastrointestinal (GI) tract, linaclotide is metabolized to a single primary active metabolite, MM-419447, which is a 13-amino acid peptide lacking the C-terminal tyrosine present in linaclotide.

2.2 Tables of Currently Available Treatments for Proposed Indications

Over-the-counter (OTC) fiber supplements, laxatives, enemas, and suppositories are frequently recommended to treat CIC and IBS-C, but are indicated only for the relief of occasional constipation. In addition, in the case of IBS-C, these treatments have not been shown to provide relief of abdominal pain, and can be associated with increased bloating, abdominal distension, and flatulence. The abdominal symptoms of IBS are treated with a variety of agents including tricyclic antidepressants, selective serotonin reuptake inhibitors, anticholinergic agents, narcotics, and non-steroidal anti-inflammatory agents. The level of evidence supporting the effectiveness of these agents for the treatment of abdominal symptoms in IBS is variable, and these agents are not indicated for the treatment of IBS.

Tegaserod maleate (Zelnorm®), another serotonin-modulating agent, was approved for constipation predominant IBS (IBS-C). However, a concerning risk of serious cardiovascular and cerebrovascular events was noted for tegaserod and marketing was voluntarily suspended in the US due to the cardiovascular effects.ⁱ It is available under Emergency IND Application only.

Lubiprostone (Amitiza®) is approved for women with IBS-C. Its effectiveness in IBS-C is based on a laxative-like effect.^{ii,iii}

There are other medications commonly used to treat IBS-C, which are not approved for an IBS indication, they are listed in Table 1 below. In addition, psychological reassurance and diet modification may be useful in controlling symptoms of IBS.

Table 1: Currently Available Treatments for IBS-C

Drug	Indication	Comments
Lubiprostone (Amitiza)	FDA approved for IBS-C in women and Chronic Idiopathic Constipation in adults	-Side effects generally include mild diarrhea and nausea. -Dyspnea may be experienced within an hour of the first dose, and may recur with repeat dosing.
Tegaserod (Zelnorm)	FDA approved for IBS-C in women and Chronic Idiopathic Constipation (CIC)	-Marketing was suspended due to severe cardiovascular side effects. -Contraindicated in patients with severe renal impairment due to increased exposure to primary metabolite -Increased events of ischemic colitis -Available under Emergency IND only
Smooth muscle relaxants ➤ Dicyclomine Hydrochloride (Bentyl) ➤ Hyoscyamine (Levsin) ➤ Chlordiazepoxide and Clidinium (Librax)	For the treatment of functional bowel/irritable bowel syndrome. DESI drugs	-Frequently prescribed for abdominal pain -Selective antimuscarinic agents unavailable in the U.S.
Tricyclic antidepressants ➤ Imipramine	Treatment of depression	Frequently prescribed for abdominal pain

Drug	Indication	Comments
<ul style="list-style-type: none"> ➤ Doxepin ➤ Desipramine ➤ Nortriptyline 	Treatment of depression	Frequently prescribed for abdominal pain
Selective serotonin reuptake inhibitors <ul style="list-style-type: none"> ➤ Citalopram (Celexa) ➤ Escitalopram (Lexapro) ➤ Fluoxetine (Prozac) ➤ Paroxetine (Paxil, Paxil CR, Pexeva) ➤ Sertraline (Zoloft) ➤ Duloxetine (Cymbalta) ➤ Venlafaxine (Effexor) 		
Laxatives <ul style="list-style-type: none"> ➤ Psyllium hydrophilic mucilloid ➤ Polyethylene glycol (PEG) ➤ Colace (OTC) 	Tx of constipation	diarrhea
Probiotics/bifido-bacteria (OTC)		Regulate bowel habits?
Fiber Supplements (OTC) Enemas (OTC) Suppositories (OTC)	Relief of occasional constipation	

2.3 Availability of Proposed Active Ingredient in the United States

Final inspections are pending as of this date.

2.4 Important Safety Issues with Consideration to Related Drugs

Linaclotide is a new molecular entity and a first-in-class small peptide molecule, and as such there are no related drugs. Because it is a peptide, allergic reactions are possible, though relatively low risk secondary to its small size and breakdown into smaller peptides and amino acids in the GI tract. See Discussion in Section 7.4.6 Immunogenicity on page 188.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

2.5.1 Meetings

IND 63,290 was submitted by Microbia, Inc. September 30, 2004 for linaclotide, a new molecular entity, for the treatment of IBS-C. Subsequently Microbia, Inc. changed names to Forest Laboratories. On September 17th, 2007 Forest Laboratories and Ironwood Pharmaceuticals entered into a (b) (4) partnership to co-develop linaclotide. Sponsorship of the IND was changed to Ironwood Pharmaceuticals on April 14, 2008. Ironwood pharmaceuticals Inc. submitted a waiver of an application user fee to FDA on May 24, 2011, under the small business waiver provision, section 736(d)(1)(D) of the Federal Food, Drug, and Cosmetic Act. On August 08, 2011, FDA has granted a small business waiver of the application fee for NDA 202-811.

The FDA has had twelve meetings and many written communications with the sponsors since IND application in September of 2004. The clinical endpoints and general trial design was agreed to in these meetings. No SPA was obtained.

2.5.2 Pediatric

Medical Officer's Comment:

Secondary to the significant findings in neonatal mouse studies, as explained below, the Division has elected to place a boxed warning in the labeling with a contraindication for pediatric patients up to age 6 and a warning to avoid use for pediatric patients 6 through 16 years of age.

Linaclotide was lethal in two separate toxicology studies in juvenile mice. The mechanism for this lethality is unknown at this time.

In an initial study, lethality was observed in juvenile mice after a single oral administration on post partum day 14 (100 mcg/kg) and post partum day 21 (600 mcg/kg). A second study showed linaclotide to be lethal at 10 mcg/kg/day in neonatal mice after oral administration of 1 or 2 daily doses starting on post partum day 7. There were no deaths in the control groups. The deaths were identified in mice with ages approximately equivalent to human infants and children age 1 to 23 months. There is currently no data for mice between ages of 21 days and 6 weeks. Linaclotide was not lethal in a study in juvenile mice age 6 weeks (approximately equivalent to humans age 12 to 16 years) at a dose of 20,000 mcg/kg/day for 28 days. While animal and human doses of linaclotide should not be compared directly for evaluating relative exposure; the maximum recommended dose in adults is approximately 5 mcg/kg/day, based on a 60-kg body weight. Therefore this finding was felt to be significant, and after consultation with the Pediatric and Maternal Health Division, and further discussion with the applicant, the decision was made to include a boxed warning with a contraindication in pediatric patients up to age 6 and a warning to avoid use in pediatric patients' age 6 through 16 in the labeling (See Section 4.3 Nonclinical/Nonclinical Pharmacology/Toxicology on page 27).

The Division chose the contraindication for age 6 to impose a wide safety margin between the possible significant risk that correlated with human ages 23 months. A warning and precaution to avoid use in pediatric patients 6 through 16 years of age is because, there is no data for mice 21 days to 6 weeks this correlates to a gap in human up to an age range of 12 to 16.

Therefore the clinical development of linaclotide in children will be placed on deferral status until results of PMRs studies to further clarify the mechanism of the deaths in neonatal/juvenile mice and their relevance to human infants.

The sponsor may initiate pediatric formulation development and an IBS endpoint evaluation instrument for use in pediatrics at this time. However, dose ranging trials and efficacy and safety trials in the pediatric population (up to age 16) will continue to be deferred until the results of the PMRs can be evaluated.

(b) (4)

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the Division will request a PMR to evaluate the mechanism of lethality seen in juvenile mice and will evaluate the results prior to approving initiation of dosing in children. The sponsor plans to submit a revised PPSR with an outline of the planned mice study in the near future.

**Pediatric Labeling:
HIGHLIGHTS OF PRESCRIBING INFORMATION**



(b) (4)

1 Page of Draft Labeling has been Withheld
in Full as b4 (CCI/TS) immediately following
this page

2.6 Other Relevant Background Information

2.6.1 Analysis of Condition

Medical Officer's Comments:

IBS-C is a significant public health concern secondary to the large population (~2% US population) that is affected with significant symptoms, the loss in productivity, and the serious, disabling symptoms in a subset of patients (~10% of IBS pop.).

Irritable bowel syndrome is a functional GI disorder characterized by recurring symptoms including abdominal pain, bloating, and abnormal defecation (constipation, diarrhea, or both) in the absence of structural or biochemical abnormalities.⁴ Irritable bowel syndrome is common in men and women, but generally more prevalent in women. The prevalence of IBS in North America appears to be 10% to 15% of the general population,^{5,6} and IBS is one of the leading reasons for consultation with a primary care physician.⁷ Although most people experience GI disturbances at some time during their lives, subjects with IBS have more frequent and severe symptoms, and are more likely to have symptoms that disrupt their work or social life.^{8,9} Rome Foundation criteria identify four subtypes of IBS: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), IBS with mixed symptoms of constipation and diarrhea (IBS-M), and unsubtyped IBS (IBS-U). Linaclotide is intended to treat patients with IBS-C.

Medical Officer's Comments:

From epidemiology consult by David Shih, MD, MS and Patty Greene, PharmD; done for NDA 21-361 for an indication for (b) (4)

Among U.S. adults, literature-based prevalence rates were about 7% for (IBS), between 1% and 2% for diarrhea-predominant IBS (IBS-D), and about 1% for constipation-predominant IBS (IBS-C). The IBS prevalence among U.S. children is not known. Only two IBS prevalence publications studied the entire United States and used the Rome II case definition published in 1999 (1), or the updated Rome III case definition, published in 2006 (2). Both studies had potential selection bias, relied on data from more than five years ago, and used Rome II case definitions.

2.6.2 Evaluation for Unmet Medical Need

Medical Officers Comments:

There is only one approved agent on the market (lubiprostone), and it is restricted to use in women for IBS-C. The other approved therapy (Zelnorm) is restricted to use in women, under emergency INDs, secondary to CV risks. The other alternative therapies available (See Table 1: Currently Available Treatments for IBS-C on page 14) are only minimally to moderately effective. Overall there is still a lack of effective therapies for all patients with IBS-C; therefore a significant unmet medical need exists.

There are other treatments for IBS-C available on the market. Lubiprostone (Amitiza) is approved for use only in *women* only with an efficacy of approximately 6% over placebo, using global endpoints for their trials. Lubiprostone has a good safety profile. Tegaserod (Zelnorm) is available under emergency IND only secondary to its withdrawal from the market because of increased cardiovascular complications and also carries increased risk for ischemic colitis including deaths. Efficacy in the controlled trials was 5-14% over placebo using global endpoints.

Other alternative, non-approved, therapies appear to be minimally to moderately effective (SSRIs, tricyclic antidepressants, laxatives, smooth muscle relaxants and probiotics). Diet modification and other therapies have proven only minimally effective. Meditation may be effective but there are no adequate trials to evaluate this intervention. Overall, there are few effective therapies for IBS-C.

2.6.3 Scientific Rational for Development

The GC-C receptor, a key regulator of intestinal function in mammals, is expressed on the epithelial cells lining the GI tract. Linaclotide, a 14-amino acid synthetic peptide, is a potent and selective GC-C receptor agonist structurally related to the endogenous guanylin peptide family. A metabolite of linaclotide, MM-419447, a 13-amino acid peptide that lacks the carboxy-terminal tyrosine of linaclotide, has been identified in all species in which linaclotide has been evaluated, including humans. The pharmacological activity and bioavailability of MM-419447 are the same as that of linaclotide. MM-419447 is the only known active metabolite and contributes to the pharmacology associated with the oral administration of linaclotide.

Both linaclotide and MM-419447 bind to and activate the GC-C receptor on the luminal surface of the intestinal epithelium, leading to an increase in intestinal secretion and GI transit, and reduction of visceral pain in animal models. Linaclotide acts within the lumen of the intestine and has very low absolute oral bioavailability ($\leq 0.2\%$ in all nonclinical species). Activation of the GC-C receptor increases cyclic guanosine

monophosphate (cGMP), both intracellularly and extracellularly. 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 fluid secretion and accelerated transit. Extracellular cGMP decreases pain-fiber activity, and may result in reduced visceral pain.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

From review by Roy Blay, Ph.D., Good Clinical Practice Assessment Branch/Division of Good Clinical Practice Compliance/Office of Scientific Investigations:

“The clinical investigator sites of Drs. Bhandari, Poch, Ringold, Horn, and Ford, were inspected in support of this NDA. A sponsor inspection of Forest Laboratories, Inc., was also conducted. Dr. Bhandari’s site was not issued a Form FDA 483. The remaining clinical sites of Drs. Poch, Ringold, Horn, and Ford and the sponsor were issued Form FDA 483s. The review division may wish to consider the limitations, if any, resulting from a lack of verification of the primary efficacy data at Drs. Bhandari and Poch’s clinical sites. To a limited extent, primary efficacy data were verified at the sites of Drs. Ringold, Horn, and Ford. The inspectional observations made at those clinical sites receiving Form FDA 483s would not appear to have a substantive effect on safety and/or efficacy evaluations. The inspection of the sponsor indicated that its procedures for collecting, handling, and archiving the large amounts of data generated by these studies appear to be adequate. Other observations noted during the inspection of the sponsor would not appear to have a substantive effect on safety and/or efficacy evaluations. Overall, the data generated by the clinical sites and submitted by the sponsor appear adequate in support of the

Table 2: Clinical Trial Sites Selected for Inspection

Site	Trial	Indication	Number subjects	Reason Site Chosen
10 Bhandari, Raj Monroe, LA, US	MCP-103-303	CIC	37	Rank #1 (both), high treatment efficacy result and high site efficacy effect size
	MCP-103-302	IBS-C	36	
61 Mark, Ringold Christiansburg, VA, US	LIN-MD-01	CIC	17	Rank #1, high site efficacy effect size, and increased number of adverse events Rank #13, high treatment efficacy result, 20% discontinued
	LIN-MD-31	IBS-C	10	
5 Arthur Pouch Shreveport , LA	MCP-103-302	IBS-C	35	Rank #3, high treatment efficacy result and high site efficacy effect size Rank #2, high treatment efficacy result and high site efficacy effect size
	MCP-103-303	CIC	37	
8 Ford, David Vaughan, ON Canada	LIN-MD-31	IBS-C	37	Rank #1, high treatment efficacy result, 60% screen success Rank #22, 23% discontinued
	LIN-MD-01	CIC	13	
95 Horn, Curtis San Antonio, TX	LIN-MD-31	IBS-C	29	Rank #2, high treatment efficacy result and high site efficacy effect size Rank #4, high site efficacy effect size
	LIN-MD-01	CIC	22	

3.2 Compliance with Good Clinical Practices

The applicant did not include an overall statement of compliance with good clinical practice; however there is a statement included with each individual trial report.

3.3 Financial Disclosures

Medical Officer's Comments:

No significant conflicts of interest were identified.

(b) (6)
➤ (b) (6), principal investigator): Received speaker payments for Savella and Fibromyalgia Educational Programs that totaled approximately \$77,550 during the reporting period. This investigator signed a memo attesting that potential bias on her part would be minimized as her speaking engagements do not affect her performance as a principal investigator, and information presented in speaking engagements is limited to materials provided by the Sponsor.

➤ (b) (6) principal investigator): Received speaker payments for Savella and Fibromyalgia Educational Programs that totaled approximately \$63,250 during the reporting period. This investigator signed a memo attesting that potential bias on her part would be minimized as her speaking engagements do not affect her performance as a principal investigator, and information presented in speaking engagements is limited to materials provided by the Sponsor.

(b) (6)
➤ (b) (6), sub-investigator): Received speaker payments for Savella Educational Programs that totaled approximately \$91,500 during the reporting period. This investigator stated that he is offered honoraria for on-label talks, which is unrelated to the study research protocol, design or analysis.

➤ (b) (6), sub-investigator): Received speaker payments for Savella Educational Programs that totaled approximately \$103,200 as of 21MAR2011. This investigator stated that he is offered honoraria for on-label talks, which is unrelated to the study research protocol, design or analysis

(b) (6)
➤ (b) (6), principal investigator): Received payments for providing consulting and writing services in support of Ironwood's gastroenterology programs that totaled \$39,330 during the reporting period (up to 1 year post-completion of the study). Also the terms of the consulting agreement between Ironwood and (b) (6) dated October 27, 2008, he was granted a stock option on November 25, 2008, for the right to purchase up to 20,000 shares of Ironwood's Series B common stock, subject to vesting over time based on (b) (6) continued service to Ironwood, at an exercise/purchase price of \$4.98 per share, which was the fair market value of the stock on the grant date.

At the agreement of both parties, the stock option was subsequently canceled in its entirety on October 22, 2009, prior to the vesting or purchase of any shares. (b) (6) consulting services agreement with Ironwood and subsequent compensations summarized above were initiated (October 2008) at least 6 months after completion of his participation of (b) (6)

(b) (6), sub-investigator): Received speaker payments for Lexapro Educational Programs that totaled approximately \$75,700 during the reporting period.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See Review by Jane L Chang, PhD., Office of New Drug Quality Assessment - Division of New Drug Quality Assessment II - Branch IV:

“This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. However, labeling issues are still pending and a site recommendation from the Office of Compliance has not been made as of the date of this review (April 3rd, 2012). Therefore, from the ONDQA perspective, this NDA is not recommended for approval per 21 CFR 314.125(b)(6),(13) in its present form until all issues are resolved.

The capsules are packaged in HDPE bottles with silica gel desiccant and capped with aluminum (b) (4) sealed (b) (4) cap. Linaclotide capsules should be kept in the original container with the desiccant to prevent degradation from moisture.

Linaclotide 145 µg and 290 µg strength capsules are recommended for approval from a Biopharmaceutics standpoint per review by Kareen Riviere, PhD.”

4.2 Clinical Microbiology

No review necessary - oral drug.

4.3 Nonclinical Nonclinical Pharmacology/Toxicology

See nonclinical review by Yuk-Chow Ng, Ph.D.

Medical Officer's Comment:

The preclinical data generally shows low toxicity except that linaclotide was lethal after a single oral administration at low doses in neonatal/juvenile mice. The lethality of linaclotide was increased with decreasing age. The minimum lethal dose in 7-day old mice was only 2 times the maximum recommended dose in adults, based on a mcg/kg comparison. Although the mortality findings in mice do not raise a concern for the use of linaclotide in adult patients, there is a concern for potential off-label use in infants or very young pediatric patients. Therefore the labeling will carry a boxed warning with a contraindicated in pediatric patients' up to age 6 and a warning to avoid use in pediatric patients' 6 through 16 years of age.

Based on the nonclinical study results, the risk of reproductive or developmental toxicity in humans is considered to be low. However, because animal reproduction studies are not always predictive of human responses, the actual risk of linaclotide during pregnancy in humans is unknown. In addition, it is not known whether linaclotide is excreted in human milk. Therefore the pregnancy category in the labeling will be changed to Category C.

Following oral dosing, linaclotide is minimally absorbed in all studied species, including mice, rats, and monkeys, with a low absolute oral bioavailability in all animal species. Plasma concentrations of linaclotide and its active primary metabolite, MM-419447, were not generally measurable in humans, consistent for a peptide with a low permeability profile. Studies have demonstrated that orally dosed linaclotide is cleared through proteolytic degradation in the intestine, which is typical of small peptides. Linaclotide is stable in acidic environments such as the stomach; however, upon reaching the intestine, linaclotide is readily metabolized to MM-419447, which is formed by the enzymatic cleavage of the C-terminal tyrosine of linaclotide. The degradation pathway of linaclotide and MM-419447 initiates

(b) (4)

Orally and intravenously administered linaclotide given as repeated daily doses were, in general, well tolerated across all species with the primary effects observed related to reversible stool consistency changes in monkeys and consistent with the exaggerated pharmacological effects of linaclotide. Although systemic exposure to linaclotide was low, consistent with a minimally absorbed peptide, toxicokinetic analyses demonstrated

that at high doses, exposure generally increased with increasing dose with no consistent gender differences between males and females. However, systemic exposure to linaclotide or its primary metabolite MM-419447 did not appear to be related to measurable toxicity in nonclinical toxicity studies. Mortality associated with linaclotide administration in monkeys was related to exaggerated pharmacologic effects (diarrhea) and the resulting dehydration. Linaclotide-related microscopic findings of submucosal inflammation in the GI tract were observed in monkeys and mice at dose levels which produced mortality. None of the microscopic findings (GI tract, heart, kidney, lymphoid system) observed in the 13-week study in mice were observed in the 26-week study in mice, even though mortality occurred at the high dose level in both studies.

The results from in vitro bacterial and mammalian cell genetic toxicity studies and in vivo carcinogenicity studies indicated that linaclotide is not mutagenic, clastogenic or carcinogenic. In the 2-year carcinogenicity studies, linaclotide was not found to be carcinogenic when administered at oral doses of up to 6000 and 3500 ug/kg/day in mice and rats, respectively, which are calculated to be up to 97-fold and 114-fold the highest proposed commercial dose adjusted for body surface area.

In reproductive toxicity studies, linaclotide was evaluated in a segment 1 fertility and early embryonic developmental study in rats. Male and female rats were dosed orally with 10, 50, or 100 mg/kg/day linaclotide. Males were dosed for 29 days prior to mating, during mating, and until necropsy. Females were dosed for 14 days prior to mating, during mating, and up to gestation day 7. Linaclotide produced no adverse effects in the mated males and females, no effects on mating or fertility, and no effects on early embryonic development. The NOAEL was considered to be ≥ 100 mg/kg/day.

Based on the nonclinical study results, the risk of reproductive or developmental toxicity in humans is considered to be low. However, because animal reproduction studies are not always predictive of human responses, the actual risk of linaclotide during pregnancy in humans is unknown. In addition, it is not known whether linaclotide is excreted in human milk. Given the low oral bioavailability and low permeability coefficients of linaclotide, it is unlikely that measurable active peptide would be present in the milk of lactating women.

Studies in juvenile animals indicated that linaclotide tolerability was related to dose as well as age of the animals. In juvenile mice, higher dose levels of linaclotide were tolerated when animals were older (post partum day 21 compared to post partum day 7). At the maximum tolerated doses, there were no effects on physical development or neurobehavioral assessments after linaclotide was administered beginning on post partum Day 9 and continuing for 9 weeks until the animals were mature. The increased sensitivity of juvenile mice to linaclotide may be related to the increased expression of intestinal GC-C receptors in young animals, or possibly to other factors such as those related to an immature GI system. Based on these nonclinical data, very young pediatric

patients may be extremely sensitive to the effects of orally administered linaclotide and the sensitivity may decrease with age.

The nonclinical NOAELs identified in the chronic toxicity studies (26-week study in mice and 39-week study in monkeys) are > 300-fold higher and in the carcinogenicity studies are approximately 100-fold higher compared to the highest proposed commercial dose. In the reproductive and developmental toxicity studies, the nonclinical NOAELs identified are > 80-fold higher compared to the highest proposed commercial dose. Even after intravenous administration of linaclotide to maximize systemic exposure, the nonclinical NOAELs identified were > 100-fold higher than the highest proposed commercial dose administered orally.

4.4 Clinical Pharmacology

Medical Officer's Comments:

See clinical pharmacology review by Sandhya Apparaju, PhD.

Linaclotide for CIC and IBS-C is acceptable from a Clinical Pharmacology perspective.

Linaclotide has low systemic availability following oral administration and is metabolized within the gastrointestinal tract, and has no known drug/drug interactions.

Systemic exposure to linaclotide and its active metabolite MM-419447, which is formed in all species studied, is minimal following oral administration of linaclotide. Thus, all in vivo studies required highly sensitive analytical methods for the detection and quantification of linaclotide and MM-419447. Liquid chromatography with tandem mass spectrometry (LC/MS/MS) was used in the majority of studies, including those in humans, as it was the most sensitive technique and the only one capable of detecting the metabolite. A radioimmunoassay (RIA) was used in a number of nonclinical in vitro studies and produced similar results for linaclotide detection.

4.4.1 Mechanism of Action

Linaclotide and its primary metabolite, MM-419447, activate the GC-C receptor, resulting in an increase in intracellular and extracellular concentrations of cGMP. The intracellular increase in cGMP following GC-C receptor activation results in the activation of the CFTR channel, which in turn causes secretion of chloride and bicarbonate into the intestinal lumen accompanied by increased fluid secretion.

In addition to the effects on intestinal secretion and GI transit, linaclotide has been shown to reduce visceral pain in animals. Linaclotide produced antinociceptive effects in all models tested, without affecting colonic tone. Linaclotide activation of the GC-C receptor results in increased levels of extracellular cGMP, which may mediate the effects on visceral pain.

4.4.2 Pharmacodynamics

Single (29 ug to 2897 ug) and repeated doses (29 ug to 966 ug) of linaclotide softened stools and decreased straining in healthy subjects relative to placebo, with more profound effects noted following doses \geq 290 ug. In a food-effect study, IBS-C patients treated for seven days with once-daily linaclotide (290 ug) administered after a high-fat breakfast had looser stools (increased BSFS score) and increased stool frequency compared with fasted patients, suggesting that food increases the PD of linaclotide. In addition to its effects on bowel habit parameters, the PD effects of linaclotide on GI function were determined in IBS-C patients by measuring intestinal transit using radiographic techniques and were found to increase colonic transit. The once-daily oral administration of linaclotide (97 ug or 966 ug) to IBS-C patients softened stools (increased BSFS score), increased stool frequency, improved ease of passage, and decreased time to first bowel movement, with a dose response for stool consistency.

4.4.3 Pharmacokinetics

Absorption and Distribution

Caco-2 cell monolayer studies have indicated that linaclotide has a low permeability coefficient in vitro and is minimally absorbed across the intestinal epithelial layer. Accordingly, linaclotide concentrations in circulation following oral dosing are very low. Studies in rats have demonstrated that plasma concentrations of linaclotide and MM-419447 are low in the jugular and portal vein, indicating that both peptides are poorly absorbed and hepatic exposure to each is minimal after oral dosing. In mice, linaclotide was not detectable in brain, liver, or adipose tissues throughout 26 weeks of once-daily oral administration of linaclotide at dose levels at least 1280 times the maximum clinical dose, adjusted for body surface area. Additionally, there was no detectable metabolite in brain or adipose tissues (liver could not be evaluated). These data, combined with the generally undetectable concentrations of linaclotide in human plasma, suggest that the distribution of linaclotide and MM-419447 into human tissues is likely to be undetectable.

Metabolism

As expected for a peptide, in vitro studies show that linaclotide is not a substrate, inhibitor or inducer of cytochrome P450 enzymes. Peptides are typically degraded by proteolytic enzymes in the GI tract, and thus the metabolism and degradation of linaclotide were elucidated through a series of nonclinical and in vitro studies using the intestinal contents of rodents and humans. Proteolytic cleavage of the C-terminal tyrosine of linaclotide in the intestine yields the only active metabolite, MM-419447, a 13-amino acid GC-C receptor agonist with the same pharmacological properties as linaclotide. In vitro results using reconstituted intestinal fluid from human cadavers suggest that the metabolism and degradation pathway of linaclotide and MM-419447 in humans (b) (4)

Given the low systemic exposure to linaclotide and MM-419447 in humans, the rapid digestion of both active peptides in the intestine, and the inherent difficulty in interpreting a mass balance study in which radiolabeled amino acids have been broken down into naturally occurring amino acids available for absorption and recycling into endogenous peptides and proteins, a traditional radiolabeled mass balance study was not conducted in humans. The decision not to conduct these studies is supported by the International Conference on Harmonization (ICH) guidelines for peptides.

Excretion

Nearly all orally dosed linaclotide is cleared via metabolism and degradation in the lumen of the intestine. During a fecal-recovery study in healthy subjects, only a small proportion of orally administered linaclotide was excreted as the active metabolite (MM-419447) in the feces, with a median recovery of 3 to 5%. Clinical studies assessing other methods of excretion have not been conducted in humans, due to the minimal systemic availability of linaclotide. A study in healthy and nephrectomized rats intravenously dosed with linaclotide identified the kidney as the primary clearance organ for any active peptide in systemic circulation, with biliary clearance likely serving as a secondary pathway.

Drug-Drug Interactions

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

Special Populations

Due to the lack of measurable concentrations of linaclotide and MM-419447 in systemic circulation following oral dosing, clinical studies in special populations, such as patients with renal or hepatic impairment, were not believed to be informative and, therefore, were not conducted. Nonclinical studies have shown that systemic linaclotide and its metabolite are cleared by at least two pathways (renal and biliary). In addition, the metabolism of linaclotide occurs outside the liver, and changes in liver function in patients would not be expected to alter linaclotide clearance. Therefore, the risk of drug-drug interactions or altered clearance in renally or hepatically impaired patients is minimal.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3: Table of Clinical Studies/Trials

<i>Type of Study</i>	<i>Study Identifier</i>	<i>Objective(s) of the Study</i>	<i>Study Design and Type of Control</i>	<i>Test Product(s)a; Dosage Regimen; Route of Administration</i>	<i>Number of Subjects^b</i>	<i>Healthy Subjects or Diagnosis of Patients</i>	<i>Duration of Treatment</i>	<i>Study Status; Type of Report</i>
<i>Biopharmaceutical Studies</i>								
Safety, PK, and PD	MCP-103-103-CSR-01	Evaluation of safety and PD effect of multiple doses of Lin on fed and fasting subjects	Phase 1, R, OL, CO (F/F)	290, 2897 ug Lin; once daily; multiple oral dose (capsule)	19	Healthy subjects	15 days (14 days Lin 290 ug + 1 day Lin 2897 ug)	Complete; Full CSR
Method Development History	BAS-103-005-MRQ-02	Summarize Lin bioanalytical method development	--	--	--	--	--	Complete; Method Development Report
Method Validation	MNP-103-004-MVR-01	Validate human plasma assay method used for analyzing human samples (from MCP-103-001 and MCP-103-002)	LC/MS/MS Assay	--	--	--	--	Complete; Method Development Report

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Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s)a; Dosage Regimen; Route of Administration	Number of Subjects_b	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Method Validation	MNP-103-043-MVR-03	Validate human plasma assay method used for analyzing human samples (from MCP-103-302, LIN-MD-01, and LIN-MD-31)	LC/MS/MS Assay	--	--	--	--	Complete; Method Development Report
<i>Studies Pertinent to Pharmacokinetics Using Human Biomaterials</i>								
Metabolism	MDP-103-056-IAR-02	Assessment of Lin stability in human intestinal microsomes	--	12 ug/mL	--	--	--	Complete; Ironwood Departmental Report
Absorption	PRD-RPT-EXP-00031	Assessment of ability of Lin to permeate intestinal epithelial cells	--	0.24, 2.4, 24 ug/mL	--	--	--	Complete; Forest Departmental Report
Metabolism	MDP-103-041-IAR-01	Lin metabolism and degradation in the luminal contents of the human intestine	--	100 ug/mL	--	--	--	Complete; Ironwood Departmental Report
Drug-Drug Interactions	MDP-103-066-IAR-01	Assessment of the human intestinal CYP450 inhibition potential of Lin	--	0.1625 – 5.2 ug/mL	--	--	--	Complete; Ironwood Departmental Report

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<i>Type of Study</i>	<i>Study Identifier</i>	<i>Objective(s) of the Study</i>	<i>Study Design and Type of Control</i>	<i>Test Product(s)a; Dosage Regimen; Route of Administration</i>	<i>Number of Subjects^b</i>	<i>Healthy Subjects or Diagnosis of Patients</i>	<i>Duration of Treatment</i>	<i>Study Status; Type of Report</i>
Drug-Drug Interactions	MDP-103-057-IAR-01	Determination of potential P-gp substrate or inhibitory activity of Lin	--	0.12 – 24 ug/mL	--	--	--	Complete; Forest Departmental Report
Drug-Drug Interactions	MDP-103-088-IAR-01	Assessment of human liver CYP450 induction potential of Lin and MM-419447	--	0.25 – 5000 ug/mL	--	--	--	Complete; CRO Report
Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s)a; Dosage Regimen; Route of Administration	Number of Subjects ^b	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Drug-Drug Interactions	(b) (4) -03-30Sep2010	Assessment of potential for Lin and MM-419447 to exhibit efflux and uptake transporters	--	Lin: 0.153 – 15.3 ug/mL MM-419447: 0.136 – 13.6 ug/mL	--	--	--	Complete; CRO Report
Drug-Drug Interactions	(b) (4) / 21-IAR-02	Assessment of human liver CYP450 inhibition potential of Lin and MM-419447	--	0.00005 – 0.05 ug/mL	--	--	--	Complete; CRO Report

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Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s)a; Dosage Regimen; Route of Administration	Number of Subjects^b	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
<i>Human Pharmacokinetics Studies</i>								
Safety, PK, and PD	MCP-103-001-CSR-03	Evaluation of safety, tolerability, PK, and PD of single ascending dose on fasting subjects	Phase 1, R, DB, PC	29, 97, 290, 966, 2897 ug Lin, or PBO; ascending single oral dose (liquid solution)	30 (4 Lin 29 ug, 8 Lin 97 ug, 4 Lin 290 ug, 4 Lin 966 ug, 4 Lin 2987 ug, 6 PBO)	Healthy subjects	1 day	Complete; Full CSR
Safety, PK, and PD	MCP-103-002-CSR-02	Evaluation of safety, tolerability, PK, and PD of multiple ascending dose	Phase 1, R, DB, PC	29, 97, 290, 966 ug Lin, or PBO; once daily; ascending multiple oral dose (liquid solution)	48 (8 Lin 29 ug, 8 Lin 97 ug, 8 Lin 290 ug, 8 Lin 966 ug, 16 PBO)	Healthy subjects	7 days	Complete; Full CSR
Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s)a; Dosage Regimen; Route of Administration	Number of Subjects ^b	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report

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Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s)^a; Dosage Regimen; Route of Administration	Number of Subjects^b	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety Studies								
Safety and PD	MCP-103-004-CSR-01	Evaluation of safety and PD of multiple doses of Lin	Phase 2a, R, DB, PC, PG	97, 290, 966 ug Lin, or PBO; once daily; multiple oral dose (liquid solution)	42 (12 Lin 97 ug, 10 Lin 290 ug, 10 Lin 966 ug, 10 PBO)	Patients with CIC	14 days	Complete; Full CSR
Safety, Efficacy, and Dose Response	MCP-103-201-CSR-01	Evaluation of dose-ranging safety, efficacy, and dose response of multiple doses of Lin	Phase 2b, R, DB, PC, DRF, PG	72, 145, 290, 579 ug Lin, or PBO; once daily; multiple oral dose (capsule)	309 (59 Lin 72 ug, 56 Lin 145 ug, 62 Lin 290 ug, 63 Lin 579 ug, 69 PBO)	Patients with CIC	28 days	Complete; Full CSR
Efficacy and Safety	MCP-103-303-CSR-01	Evaluation of efficacy and safety of multiple doses of Lin	Phase 3, R, DB, PC, PG	145, 290 ug Lin, or PBO; once daily; multiple oral dose (capsule) with RW	643 (217 Lin 145 ug, 217 Lin 290 ug, 209 PBO)	Patients with CIC	16 weeks (12 weeks DB + 4 weeks RW)	Complete; Full CSR
Efficacy and Safety	LIN-MD-01	Evaluation of efficacy and safety of multiple doses of Lin	Phase 3, R, DB, PC, PG	145, 290 ug Lin, or PBO; once daily; multiple oral dose (capsule)	633 (213 Lin 145 ug, 205 Lin 290 ug, 215 PBO)	Patients with CIC	12 weeks	Complete; Full CSR

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Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s)a; Dosage Regimen; Route of Administration	Number of Subjects^b	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PD	MCP-103-005-CSR-01	Evaluation of dose-ranging PD of multiple doses of Lin	Phase 2a, R, DB, PC, PG	97, 966 ug Lin, or PBO; once daily; multiple oral dose (liquid solution)	36 (12 Lin 97 ug, 12 Lin 966 ug, 12 PBO)	Patients with IBS-C	5 days	Complete; Abbreviated CSR
Safety, Efficacy, and Dose Response	MCP-103-202-CSR-01	Evaluation of dose-ranging safety, efficacy, and dose response of multiple doses of Lin	Phase 2b, R, DB, PC, DRF, PG	72, 145, 290, 579 ug Lin, or PBO; once daily; multiple oral dose (capsule)	420 (79 Lin 72 ug, 82 Lin 145 ug, 85 Lin 290 ug, 89 Lin 579 ug, 85 PBO)	Patients with IBS-C	12 weeks	Complete; Full CSR
Efficacy and Safety	MCP-103-302-CSR-01	Evaluation of efficacy and safety of multiple doses of Lin	Phase 3, R, DB, PC, PG	290 ug Lin or PBO; once daily; multiple oral dose (capsule)	805 (402 Lin 290 ug, 403 PBO)	Patients with IBS-C	26 weeks	Complete; Full CSR
Efficacy and Safety	LIN-MD-31	Evaluation of efficacy and safety of multiple doses of Lin	Phase 3, R, DB, PC, PG	290 ug Lin or PBO; once daily; multiple oral dose (capsule) with RW	802c (406 Lin 290 ug, 396 PBO)	Patients with IBS-C	16 weeks (12 weeks DB + 4 weeks RW)	Complete; Full CSR

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Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s)^a; Dosage Regimen; Route of Administration	Number of Subjects^b	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Long-Term Safety	MCP-103-305	Evaluation of long-term safety and treatment satisfaction (additional) of multiple doses of Lin	OL, SA, LTS study	290 ug Lin (with option of reduction to 145 ug); once daily; multiple oral dose (capsule)	1725d	Patients with CIC or IBS-C	Up to 78 weeks (18 months)	Ongoing
Long-Term Safety	LIN-MD-02	Evaluation of long-term safety and treatment satisfaction (additional) of multiple doses of Lin	OL, SA, LTS study	290 ug Lin (with option of reduction to 145 ug); once daily; multiple oral dose (capsule)	1553d	Patients with CIC or IBS-C	Up to 78 weeks (18 months)	Ongoing

CIC = chronic constipation; CO = crossover; CRO = contract research organization; CSR = clinical study report; DB = double-blind; DRF = dose-range-finding;

F/F = fed/fasting; IBS-C = irritable bowel syndrome with constipation; LC/MS/MS = liquid chromatography/ tandem mass spectrometry; Lin = linaclotide;

LTS = long-term safety; OL = open-label; PBO = placebo; PC = placebo-controlled; PD = pharmacodynamics; PG = parallel-group; P-gp = P-glycoprotein;

PK = pharmacokinetics; R = randomized; RW = randomized withdrawal; SA = single-arm

a. Updated dose-strength expression based on nominal linaclotide content; see Module 2.7.1 (Summary of Biopharmaceutical Studies and Associated Analytical

Methods) for details regarding clinical dose expression changes

b. Number of subjects in the Safety Population

c. Includes 2 patients who were each randomized twice into the trial

d. Includes rollover patients (i.e., patients who completed either a Phase 2b or Phase 3 study)

5.2 Review Strategy

This NDA has two indications one for Chronic Idiopathic Constipation (CIC) and one for IBS-C. This reviewer will perform the efficacy and safety for the IBS-C indication and will perform the combined safety review for both indications. Erica Wynn, MD will perform the review for the CIC indication. The two phase 3 efficacy trial designs and individual results will be discussed in this Section, the combined efficacy results will be presented in Section 6 Review of Efficacy. The data from the two ongoing open-label long term safety trials will be discussed in Section 7 on page 115.

Note: during the course of development the analytical procedures for determining the linaclotide content have been optimized resulting in changes of the expression of the dose but not the actual dose strength of the capsules. Thus in LIN-MD-31 the dose strength was expressed as 300ug, subsequently this was updated to an expressed dose of 266ug. After completion of the trial the finalized dose expression is 290ug.

5.3 Discussion of Individual Studies/Clinical Trials

This Section will review the trial design and efficacy results of the two phase 3, pivotal clinical trials for IBS-C:

- MCP-103-302 A phase 3, randomized, double-blinded, placebo controlled, parallel-group, multi-center, 26 week treatment trial of 266ug of linaclotide daily
 - Section 5.3.1, starting on page 39.
- LIN-MD-31 – A phase 3, randomized, double-blinded, placebo controlled, multi-center, parallel-group, 12 week treatment trial of 266ug of linaclotide daily, with a 4 week randomized withdrawal
 - Section 5.3.2, starting on page 69.

Note: The efficacy results of the phase 2B dose ranging trial (MCP-103-202) will be discussed in Section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations, on page 108.

The data from the 2 long-term safety trials (MCP-103-305 and LIN-MD 02) will be discussed in Section 7 on page 115.

5.3.1 MCP-103-302-CSR-01 - Evaluation of Efficacy and Safety of Multiple Doses of Linaclotide

Medical Officer's Comments:

See discussion in Section 6 Review of Efficacy on page 93.

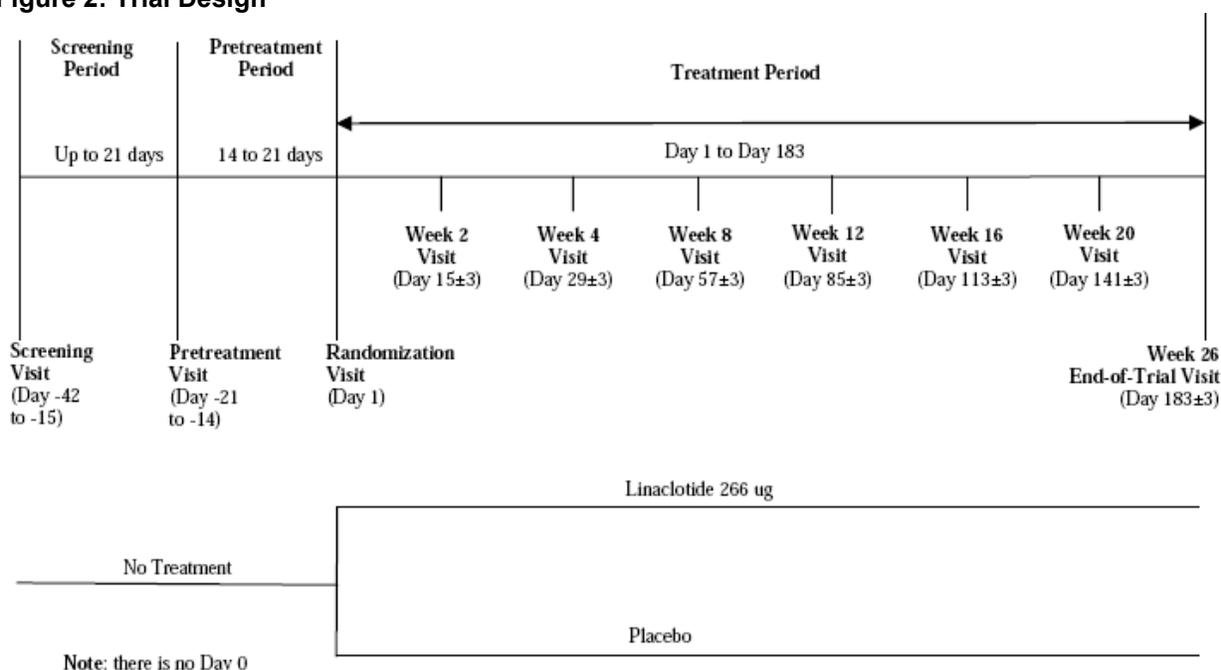
5.3.1.1 Indication

The objective of this trial is to determine the efficacy and safety of linaclotide 266ug daily administered to patients with irritable bowel syndrome with constipation (IBS-C).

5.3.1.2 Methods

Trial Design

Figure 2: Trial Design



Note: there is no Day 0

This is a double-blind, placebo-controlled, parallel-group trial design. The MCP-103-302 trial had a 14 day Pretreatment Period during which no study drug (including placebo) was administered, followed by a 26 week Treatment Period during which patients were randomized to take either active drug or placebo. The 14-day Pretreatment Period to establish a baseline without therapy and to familiarize patients with data collection methodology.

5.3.1.3 Trial Population

Enrolled patients were required to meet modified Rome II criteria for IBS-C that were similar to the modified criteria used in other IBS-C drug development programs. The modified criteria were used to recruit patients into the Phase 3 trials, rather than the

Rome III criteria, to ensure consistency between the Phase 2 and Phase 3 study populations. In addition, data demonstrate that there is a great deal of overlap in the characteristics of patients who meet the Rome II criteria versus those who meet the Rome III criteria.¹⁰

Although the criteria for IBS were explicitly followed according to Rome II, the inclusion criteria to define the constipation subtype were slightly modified by:

- Requiring all patients to have < 3 bowel movements (BMs) per week (as stool frequency was one of the parameters assessed as a primary efficacy parameter in the Phase 2 and 3 IBS-C studies) and
- Allowing no more than 25% of BMs that were loose (mushy) or watery during the 12 weeks before the screening visit (to ensure that the patient might not be converting from the IBS-C to the IBS-D subtype).

Table 4: Comparison of Rome II Criteria and the Modified Rome II Criteria used in the Linaclootide IBS-C Clinical Studies

<i>Rome II Criteria for IBS-C</i>	<i>Modified Rome II IBS-C Criteria used in Linaclootide Clinical Studies</i>
<p>At least 12 weeks or more, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has 2 out of the 3 features:</p> <ol style="list-style-type: none"> 1. Relieved with defecation, and or 2. Onset associated with a change in frequency of stool, and/or 3. Onset associated with a change in form (appearance) of stool <p>Supportive Symptoms of IBS: 1. Fewer than 3 bowel movements a week 2. More than 3 bowel movements a day</p> <ol style="list-style-type: none"> 3. Hard or lumpy stools 4. Loose (mushy) or watery stools 5. Straining during a bowel movement 6. Urgency (having to rush to have a bowel movement) 7. Feeling of incomplete bowel movement 8. Passing mucus (white material) during a bowel movement 9. Abdominal fullness, bloating, or swelling <p>Constipation-predominant: 1 or more of 1, 3, or 5 and none of 2, 4, or 6; or: 2 or more of 1, 3, or 5 and one of 2, 4, or 6.</p>	<p>Patients reported abdominal discomfort or pain that had ≥ 2 of the following features for ≥ 12 weeks, which need not be consecutive, in the 12 months preceding the Screening Visit:</p> <ol style="list-style-type: none"> a) relieved with defecation b) onset associated with a change in frequency of stool, and c) onset associated with a change in form [appearance] of stool. Patients must also have reported < 3 spontaneous bowel movements (SBMs) per week and reported ≥ 1 of the following symptoms for 12 weeks in the preceding 12 months: <ul style="list-style-type: none"> • Straining during $\geq 25\%$ of bowel movements (BMs) • Lumpy or hard stools during $\geq 25\%$ of BMs • A sensation of incomplete evacuation during $> 25\%$ of BMs <p>Patients were excluded if they reported loose (mushy) or watery stools (BSFS score of 6 or 7) in the absence of any laxative, suppository, enema, or prohibited medication for $> 25\%$ of BMs during the 12 weeks before the Screening Visit.</p>

Patients meeting the modified Rome II criteria were eligible for the Phase 3 trials if during the 2-week Pretreatment Period they met all of the following criteria:

- An average score for Abdominal Pain at its Worst of ≥ 3.0 on a 0-to-10-point numerical rating scale (NRS)
- Less than 3 Complete Spontaneous Bowel Movements (CSBMs) per week, ≤ 5 Spontaneous Bowel Movements (SBMs) per week, no more than 1 SBM with a Bristol Stool Form Scale (BSFS) score of 6 and none with score of 7
- Compliance with the Interactive Voice Response System (IVRS) (i.e., providing adequate responses on at least 10 out of the 14 pretreatment days)

Inclusion Criteria

1. Patient signed an ICF;
2. Patient was an ambulatory, community-dwelling male or non-pregnant female and was aged 18 years or older at the Screening Visit. Lactating females agreed not to breastfeed;
3. Sexually active female patients of childbearing potential agreed to use 1 of the following methods of birth control from the date they signed the ICF until 24 hours after their final dose of study drug:
 - a. Hormonal contraception (i.e., oral contraceptive, contraceptive implant, or injectable hormonal contraceptive),
 - b. Double barrier birth control (e.g., condom plus intrauterine device, diaphragm plus spermicide),
 - c. Surgical sterilization (i.e., bilateral oophorectomy, hysterectomy, or tubal ligation),
 - d. Maintenance of a monogamous relationship with a male partner who had been surgically sterilized by vasectomy;
4. Females of childbearing potential must have had a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at the Randomization Visit prior to dosing
5. Patient met the colonoscopy requirements defined by the American Gastroenterological Association guidelines and described in Appendix III of the protocol. (Note: Patients were eligible to enter the Pretreatment Period on the fifth calendar day after a colonoscopy);
6. Patient had no clinically significant findings on a physical examination, 12-lead electrocardiogram (ECG), and clinical laboratory tests (clinical chemistry panel, complete blood count [CBC], urine drug screen, urinalysis [UA]) after signing the ICF but before receiving the first dose of study drug. (Note: The Investigator determined if a particular finding was clinically significant. In making this determination, the investigator considered whether the particular finding could prevent the patient from performing any of the protocol-specified assessments, could represent a condition that would exclude the patient from the trial, could represent a safety concern if the patient participated in the trial, or could confound the trial-specified assessments of safety or efficacy);

7. Patient met the Rome II criteria for IBS: reported abdominal discomfort or pain that had 2 or more of the following 3 features for at least 12 weeks, which did not need to be consecutive, in the 12 months before the Screening Visit, or before starting chronic treatment with tegaserod or lubiprostone:
 - a. Relieved with defecation,
 - b. Onset associated with a change in frequency of stool,
 - c. Onset associated with a change in form (appearance) of stool;
8. Patient reported < 3 BMs (with each BM occurring in the absence of any laxative, suppository, or enema use during the preceding 24 hours) per week and reported 1 or more of the following symptoms for at least 12 weeks, which did not need to be consecutive, in the 12 months before the Screening Visit or before starting chronic treatment with tegaserod, lubiprostone, polyethylene glycol 3350, or any laxative:
 - a. Straining during > 25% of BMs,
 - b. Lumpy or hard stools during > 25% of BMs,
 - c. Sensation of incomplete evacuation during > 25% of BMs;
9. Patient had an average score ≥ 3.0 for abdominal pain at its worst as reported in the IVRS using an 11-point numerical rating scale (NRS) during the 14 calendar days before the start of the Treatment Period;
10. Patient reported an average of < 3 complete spontaneous BMs (CSBMs) and ≤ 5 SBMs per week by the IVRS during the 14 days before the start of the Treatment Period. (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);
11. Patient was compliant with IVRS completion by adequately responding to IVRS questions on 10 or more of the 14 days before the start of the Treatment Period;
12. Patient was willing to discontinue any laxatives used before the Pretreatment Visit in favor of the protocol-defined Rescue Medicine (bisacodyl tablets or suppositories);
13. Patient was fluent in English or Spanish;
14. Patient had unrestricted access to a working touch-tone telephone for the entire trial;
15. Patient agreed to refrain from making any new, major life-style changes that may have affected IBS-C 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.

Exclusion Criteria

1. Patient reported loose (mushy) or watery stools (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;
2. Patient had a structural abnormality of the gastrointestinal (GI) tract or a disease or history of a condition that could affect GI motility;
3. Patient had ever had a diagnosis of familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, or any other form of familial colorectal cancer, or inflammatory bowel disease. Patient had a family history of familial adenomatous

- polyposis or hereditary nonpolyposis colorectal cancer or other familial form of colorectal cancer;
4. Patient currently had both unexplained and clinically significant alarm symptoms (lower GI bleeding [rectal bleeding or heme-positive stool], iron-deficiency anemia or any unexplained anemia, or weight loss) and systemic signs of infection or colitis;
 5. Patient currently had active peptic ulcer disease (i.e., disease that was not adequately treated or stable with therapy);
 6. Patient had a history of diverticulitis or a history of any chronic condition (e.g., chronic pancreatitis, polycystic kidney disease, ovarian cysts, endometriosis, lactose intolerance) that could be associated with abdominal pain or discomfort and could confound the assessments in this trial;
 7. Patient had a potential central nervous system cause of constipation (e.g., Parkinson's disease, spinal cord injury, and multiple sclerosis);
 8. Patient had ever had any of the following diseases or conditions that could be associated with constipation: pseudo-obstruction, colon inertia, megacolon, megarectum, bowel obstruction, descending perineum syndrome, solitary rectal ulcer syndrome, systemic sclerosis;
 9. Patient had ever had a 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);
 10. Patient had had surgery that met any of the following criteria:
 - a. Bariatric surgery for treatment of obesity, or surgery to remove a segment of the GI tract at any time before the Screening Visit,
 - b. Surgery of the abdomen, pelvis, or retroperitoneal structures during the 6 months before the Screening Visit,
 - c. An appendectomy or cholecystectomy during the 60 days before the Screening Visit,
 - d. Other major surgery during the 30 days before the Screening Visit;
 11. Patient had a 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);
 12. Patient had a history of diabetic neuropathy;
 13. Patient had 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;
 14. Patient had a recent history (during the 12 months before the Randomization Visit) of drug or alcohol abuse. (Note: Patients with a history of drug or alcohol abuse that was diagnosed greater than 12 months before the Randomization Visit could be enrolled as long as they have exhibited no actual abuse during the 12 months before the Randomization Visit);

15. Patient reported a BSFS score of 6 (loose, mushy stools) for > 1 SBM or a BSFS score of 7 (watery stools) with any SBM during the 14 days before the start of the Treatment Period;
16. 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., before the Randomization Visit);
17. Patient 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 defined in Appendix II of the protocol. (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);
18. Patient had been hospitalized for a psychiatric condition or had made a suicide attempt during the 2 years before the Randomization Visit;
19. Patient had received an investigational drug during the 30 days before the Screening Visit or was planning to receive an investigational drug (other than that administered during this trial) or use an investigational device at any time during the trial;
20. Patient had an acute or chronic condition that, in the investigator's opinion, would limit the patient's ability to complete or participate in this clinical trial;
21. Patient had been randomized into any Phase 1 or Phase 2 study in which linaclotide was a treatment (Patients who enrolled into these studies but failed to be randomized were eligible for the current trial.) or had previously entered the Pretreatment Period of this trial or any other Phase 3 trial in which linaclotide was a treatment;
22. Patient was involved in the conduct and administration of this trial as an investigator, subinvestigator, trial coordinator, or other trial staff member, or the patient was a first degree family member, significant other, or relative residing with 1 of the above persons involved in the trial;
23. Patient was active in the Screening or Pretreatment Period after the closure of enrollment date identified by the Sponsor (Note: Patients active in the Screening or Pretreatment Period could be considered for participation in MCP-103-305, subject to meeting that protocol's inclusion and exclusion criteria).

5.3.1.4 Subject Disposition

A total of 2340 patients were screened; 488 patients were screen failures and 1047 patients were pretreatment failures (Table 5). A total of 805 patients provided informed consent, successfully completed Screening and the Pretreatment Period, and were randomized to treatment. Of the 805 randomized patients, 599 (74%) completed the Treatment Period per protocol requirements. A total of 206 (26%) patients withdrew from the trial during the 26-week Treatment Period, with a similar percentage of withdrawals in the linaclotide and placebo groups (26.9% versus 24.3%; $p = 0.4201$). A higher percentage of patients treated with linaclotide as compared with placebo discontinued due to an adverse event (10.2% versus 2.5%; $p < 0.0001$). A lower

percentage of patients treated with linaclotide as compared with placebo discontinued due to insufficient therapeutic response (3.7% versus 8.2%; $p = 0.0107$).

Table 5: Reason for Screen and Pretreatment Failures - Screened Population

	Total (N=2340) n (%)
Screen Failures [1]	488 (20.9)
Did not Meet Inc/Exc Criteria	336 (14.4)
Adverse Event	2 (0.1)
Protocol Violation	8 (0.3)
Withdrawal of Consent	91 (3.9)
Lost to Follow-up	22 (0.9)
Other	29 (1.2)
Pretreatment Failures [2]	1047 (44.7)
Did not Meet Inc/Exc Criteria	893 (38.2)
Adverse Event	3 (0.1)
Protocol Violation	6 (0.3)
Withdrawal of Consent	103 (4.4)
Lost to Follow-up	27 (1.2)
Other	15 (0.6)

N = Number of screened patients, patients who were re-screened are only counted once.

n = Number of patients within a specific category.

[1] Screen Failures are patients who sign an Informed Consent Form (ICF) but do not qualify for inclusion into the study based on their Screening Visit (Visit 1) evaluations. Patients who were re-screened and failed both times during the screening period were only counted once and the most recent reason of failure was captured in the table.

[2] Pretreatment failures are patients who sign an ICF, enter the pretreatment period but are not randomized into the study.

Patients who were re-screened and who failed once during the screening period and once during pretreatment are counted only in the pretreatment failure category.

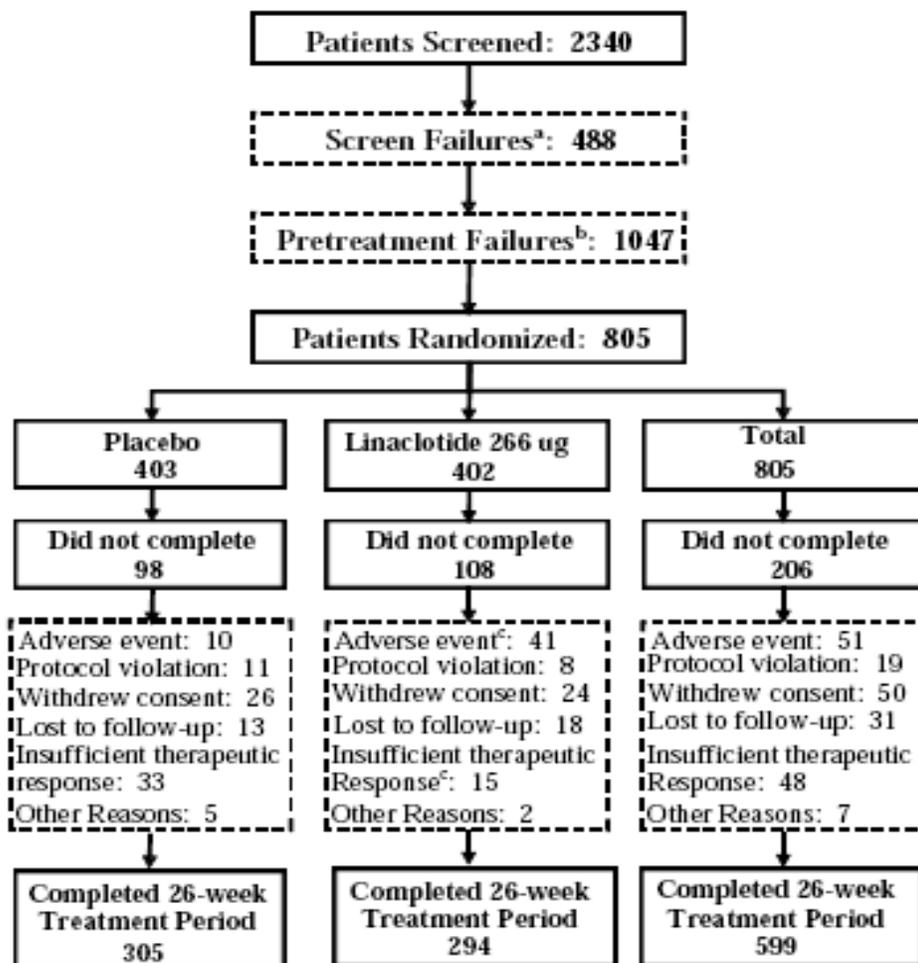
Patients who were re-screened and became randomized are not counted in either one of the failure categories.

Protocol Deviations

As directed by the ICH Clinical Report Guidelines, protocol deviations are been summarized according to the following broad classes:

1. Those patients who entered the trial even though they did not satisfy the entry criteria (numbering 38)
2. Those patients who developed withdrawal criteria during the trial but were not withdrawn (none)
3. Those patients who received the incorrect dose (numbering 6)
4. Those patients who received an excluded concomitant treatment (numbering 274)

Figure 3: Patient Disposition (Treatment Period) MCP-103-302



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 based on their Screening Visit (Visit 1) evaluations. Patients who were re-screened and failed the second time during the Screening Period were only counted once and the most recent reason of failure was captured. Patients who were re-screened and randomized were not counted in either one of the failure categories. b. Patients who signed an ICF, entered the Pretreatment Period, but were not randomized into the trial. c. $p < 0.0001$ for discontinuation due to adverse event (41 linaclotide-treated patients versus 10 placebo treated patients) and $p = 0.0107$ for discontinuation due to insufficient therapeutic response (15 linaclotide treated patients versus 33 placebo-treated patients), from comparison of the linaclotide group versus the placebo group using Fisher's exact test. All other comparisons had p -values > 0.05 (Section 14, Table 14.1.3).

5.3.1.5 Demographics

For the ITT Population, the majority of patients were Caucasian (78.0%) and female (89.6%). The treatment groups were generally balanced with respect to baseline demographics and other baseline characteristics. Mean patient age overall was 44.3 years; means for the individual dose groups were 44.0 years for the placebo group and

44.6 years for the linacotide group. Forty patients (5.0%) were ≥ 65 years of age. African American patients comprised 18.4% of the trial population; 10.1% of patients reported Hispanic/Latino ethnicity. More patients were male in the placebo group (51 patients, 12.7%) compared to the linacotide group (33 patients, 8.2%) (p = 0.0379).

Table 6: Demographic and Baseline Characteristics (ITT Population) - MCP-103-302

Demographic Characteristic	Placebo (N=403)	Linacotide (N=401)	Total (N=804)	p-value
Age, years				
Mean (SD)	44.0 (13.4)	44.6 (13.1)	44.3 (13.3)	0.4695
Median (Min, Max)	44.0 (18, 87)	45.0 (19, 82)	44.0 (18, 87)	
Age, n (%)				
18 to < 40 years	153 (38.0)	142 (35.4)	295 (36.7)	0.5174
40 to < 65 years	233 (57.8)	236 (58.9)	469 (58.3)	
≥ 65 years	17 (4.2)	23 (5.7)	40 (5.0)	
Gender, n (%)				
Female	352 (87.3)	368 (91.8)	720 (89.6)	0.0379
Male	51 (12.7)	33 (8.2)	84 (10.4)	
Race, n (%)				
Asian	6 (1.5)	2 (0.5)	8 (1.0)	0.5619
Black/African American	78 (19.4)	70 (17.5)	148 (18.4)	
Caucasian	311 (77.2)	316 (78.8)	627 (78.0)	
Other	8 (2.0)	13 (3.2)	21 (2.6)	
Ethnicity, n (%)				
Hispanic/Latino	38 (9.4)	43 (10.7)	81 (10.1)	0.5390
Not Hispanic/Latino	365 (90.6)	358 (89.3)	723 (89.9)	
Height, cm				
Mean (SD)	165.8 (7.8)	164.7 (7.9)	165.2 (7.9)	0.0343
Median (Min, Max)	165.1 (139.7, 193.0)	165.1 (134.6, 188.0)	165.1 (134.6, 193.0)	
Weight, kg				
Mean (SD)	76.4 (18.4)	75.5 (18.1)	75.9 (18.3)	0.4924
Median (Min, Max)	73.0 (43.9, 142.5)	72.1 (43.6, 173.6)	72.6 (43.6, 173.6)	
BMI, kg/m²				
Mean (SD)	27.7 (6.2)	27.8 (5.9)	27.7 (6.1)	0.9348
Median (Min, Max)	26.5 (16.4, 54.2)	26.6 (17.7, 51.0)	26.6 (16.4, 54.2)	

Data Source: Section 14, Table 14.2.2

Age was calculated up to the informed consent date. p-values for continuous variables (e.g., age, weight, height, BMI) were from an ANOVA with treatment group and region as factors; p-values for categorical variables (e.g., sex, ethnicity, and race) were from a CMH test controlling for geographic region.

SD = Standard Deviation, Min = Minimum, Max = Maximum, BMI = Body mass index, defined as weight in kg divided by height in M².

Table 7: Baseline Efficacy Parameters (ITT Population)

Efficacy Parameter	Statistic	Placebo (N=403)	Linaclotide (N=401)	Total (N=804)	p-value
Weekly CSBM Rate	n	403	401	804	0.2080
	Mean (SD)	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)	
	Median	0.0	0.0	0.0	
	Min, Max	0.0, 2.9	0.0, 2.4	0.0, 2.9	
Weekly SBM Rate	n	403	401	804	0.9748
	Mean (SD)	1.7 (1.4)	1.7 (1.4)	1.7 (1.4)	
	Median	1.5	1.5	1.5	
	Min, Max	0.0, 5.4	0.0, 5.8	0.0, 5.8	
Stool Consistency (BSFS)	n	344	342	686	0.2499
	Mean (SD)	2.3 (1.0)	2.4 (1.1)	2.3 (1.0)	
	Median	2.0	2.0	2.0	
	Min, Max	1.0, 6.0	1.0, 6.0	1.0, 6.0	
Straining	n	344	342	686	0.6346
	Mean (SD)	3.5 (0.8)	3.6 (0.8)	3.6 (0.8)	
	Median	3.6	3.6	3.6	
	Min, Max	1.0, 5.0	1.0, 5.0	1.0, 5.0	
Abdominal Pain	n	403	401	804	0.4525
	Mean (SD)	5.5 (1.7)	5.6 (1.7)	5.6 (1.7)	
	Median	5.3	5.4	5.4	
	Min, Max	2.9, 10.0	2.9, 10.0	2.9, 10.0	
Percent of Abdominal Pain Free Days	n	403	401	804	0.9702
	Mean (SD)	2.1 (6.3)	2.1 (7.0)	2.1 (6.7)	
	Median	0.0	0.0	0.0	
	Min, Max	0.0, 57.1	0.0, 53.8	0.0, 57.1	
Abdominal Discomfort	n	403	401	804	0.2282
	Mean (SD)	6.0 (1.7)	6.1 (1.7)	6.1 (1.7)	
	Median	5.8	6.1	5.9	
	Min, Max	2.1, 10.0	2.5, 10.0	2.1, 10.0	
Bloating	n	403	401	804	0.2304
	Mean (SD)	6.5 (1.8)	6.6 (1.9)	6.6 (1.8)	
	Median	6.5	6.6	6.6	
	Min, Max	1.6, 10.0	0.0, 10.0	0.0, 10.0	

Data Source: Section 14, Table 14.2.4

Baseline efficacy values are derived from the IVRS data collected daily 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.

The most frequently reported body systems in which patients reported a notable medical history were surgical and medical procedures (602 patients, 74.8%) and gastrointestinal disorders (502 patients, 62.4%). Other body systems in which a notable medical history was reported included psychiatric (351 patients, 43.6%) and nervous system disorders (328 patients, 40.7%).

Overall, concomitant medication use appeared to be similar between the placebo and linaclotide groups. Use was similar for Proton Pump Inhibitors (PPI's), Selective Serotonin Reuptake Inhibitors (SSRI's) and other antidepressants, as well as benzodiazepines and related drugs. However, the percentage of patients using propionic acid derivatives (NSAIDs) as concomitant medications was higher in the placebo group than in the linaclotide group (21.8% versus 16.4%). Four patients used the propionic acid derivative to treat their abdominal pain (2 patients in the placebo group).

Treatment compliance was > 96% for both treatment groups during the Treatment Period overall (97.2% and 96.8% in the placebo and linaclotide groups, respectively). The compliance rate remained above the 96% level for both groups throughout each of the compliance periods (Weeks 1-4, 5-8, 9-12, 13-16, 17-20, and 20-26).

Drug Exposure

In the 26-week trial, the mean treatment duration was 148.8 days for linaclotide 290 ug, versus 152.6 days for placebo.

5.3.1.6 Efficacy Assessments

The Screened Population included 2340 patients who had a Screening Visit and were assigned a PID number

The Randomized Population included 805 patients who were randomized to a treatment group at the Randomization Visit

The Safety Population included 805 patients who received ≥ 1 dose of double-blind study drug during the Treatment Period

The ITT Population included 804 patients who were in the Safety Population and had ≥ 1 post-randomization entry of the primary efficacy assessment (i.e., an assessment of abdominal pain at its worst or the daily IVRS information that determined whether an SBM was a CSBM).

Statistical Assessment Plan

The primary analysis and all secondary and additional analyses for the Treatment Period were performed on the ITT Population.

An observed cases (OC) approach to missing post-baseline data was applied (i.e., a patient's missing values were not imputed). Any diminished treatment group sample sizes in the analyses represent missing observations for the calculated parameters because only observed cases were used in the calculation. That is, variations in trial participation (e.g., patients who withdrew, variability in IVRS compliance) affected the number of observations used in the analysis of specific parameters. For example, if no

SBM occurred for a patient for a given period such as the Pretreatment Period, the corresponding SBM-dependant parameters (e.g., Straining and Stool Consistency) could not be calculated for the Treatment Period.

In addition, as sensitivity analyses, the corresponding weekly analyses were performed using both the OC and an LOCF.

The overall type I family-wise error rate for testing the primary and secondary efficacy parameters was controlled at the 0.05 significance level using a 5-step serial gatekeeping multiple comparisons procedure (MCP). All confidence intervals were 2-sided 95% confidence intervals

Nominal p-values unadjusted for multiplicity are presented for all analyses. However, for each of the primary and secondary efficacy parameters, the result was considered statistically significant only if the corresponding MCP criteria were met. There were 4 primary efficacy parameters and 10 secondary efficacy parameters. After applying the pre-specified MCP, all 14 comparisons were statistically significant

The primary efficacy parameters consisted of two components:

- 1) Abdominal Pain at its Worst and
- 2) Complete Spontaneous Bowel Movements (CSBMs).

The daily patient assessments used to determine the primary efficacy parameter were as follows:

Daily Patient Assessment of Abdominal Pain at its Worst

Patient assessment of Abdominal Pain at its Worst was collected daily by IVRS calls. The rating of Abdominal Pain at its Worst 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 pain at its worst over the last 24 hours? Enter a number from 0 to 10, where 0 represents no abdominal pain and 10 represents very severe abdominal pain."

Spontaneous Bowel Movement (SBM) and Complete Spontaneous Bowel Movement (CSBM)

An SBM was a BM that occurred in the absence of laxative, suppository, or enema use on the calendar day of the BM or the calendar day before the BM. A CSBM was an SBM that was associated with a sense of complete evacuation.

There were 4 primary efficacy parameters:

- 1) 9/12 Week APC 3+1 Responder
 - 9 of 12 Weeks, $\geq 30\%$ reduction in mean Abdominal Pain from baseline **and** Complete Spontaneous Bowel Movement (APC), at least 3 CSBMs per week, with an increase of 1 CSBM per week over baseline, Responder

- 2) 9/12 Week CSBM 3+1 Responder
 - CSBM 3+1 Responders for at least 9 of the first 12 weeks of the Treatment Period

- 3) 9/12 Week Abdominal Pain Responder
 - 9 Of 12 weeks with at least a 30% reduction in mean abdominal pain score from baseline

- 4) 6/12 week APC +1 Responder
 - 6 of 12 Weeks, ≥ 30% reduction in mean Abdominal Pain from baseline **and** with an increase of 1 CSBM per week over baseline responder

5.3.1.7 Analysis of Primary Endpoint(s)

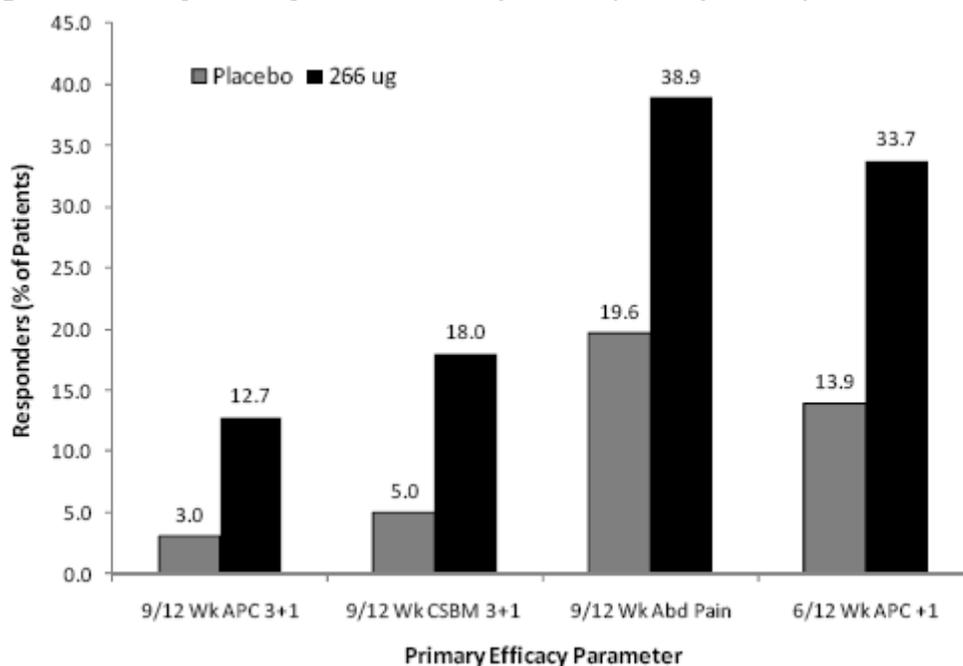
Table 8: Overview of Primary Efficacy Results ITT Population - MCP-103-302

Parameter	Placebo (N=403)	Linaclotide (N=401)
Primary Efficacy Parameters		
9/12 Week APC 3+1 Responder Responder, n (%) Odds Ratio (95% CI)	12 (3.0)	51 (12.7) ^a 4.7 (2.4, 8.8)
9/12 Week CSBM 3+1 Responder Responder, n (%) Odds Ratio (95% CI)	20 (5.0)	72 (18.0) ^a 4.2 (2.5, 7.0)
9/12 Week Abdominal Pain Responder Responder, n (%) Odds Ratio (95% CI)	79 (19.6)	156 (38.9) ^a 2.6 (1.9, 3.6)
6/12 Week APC +1 Responder Responder, n (%) Odds Ratio (95% CI)	56 (13.9)	135 (33.7) ^a 3.2 (2.2, 4.5)

Data Source: Section 14, Tables 14.4.1.1A, 14.4.1.2A, 14.4.1.3A, 14.4.1.4A, 14.2.4, and 14.4.2.1A to 14.4.2.10A
 Baseline is a composite of all patients.

a. p-values based on the CMH test controlling for geographic region; p < 0.0001. All p-values met the criteria for statistical significance based on the MCP.

Figure 4: Primary Efficacy Parameter Responders (ITT Population)



p-values were obtained from the CMH tests controlling for geographic region, comparing linaclotide versus placebo; all p-values were < 0.0001 and met the criterion for statistical significance based on the MCP.

The number and percentage of patients who were 9/12 week APC 3+1 Responders were 51 patients, 12.7% for the linaclotide group and 12 patients, 3.0% for the placebo group with an odds ratio of 4.65 ($p < 0.0001$).

Table 9: Primary Efficacy Analysis: 9/12 Week APC 3+1 Responders (ITT Population)

Description	Placebo (N=403) n (%)	Linaclotide (N=401) n (%)
Responder	12 (3.0)	51 (12.7)
Non-Responder	391 (97.0)	350 (87.3)
Difference in Responder Rate (Linaclotide - Placebo)	9.7	
Odds Ratio for Response (Linaclotide : Placebo)	4.65	
95% CI for Odds Ratio	(2.44, 8.84)	
p-value	< 0.0001	

Data Source: Section 14, Table 14.4.1.1A

A 9/12 week APC 3+1 responder was a patient who met the weekly APC 3+1 responder criteria for at least 9 of the first 12 weeks of the Treatment Period.

n = Number of patients within a specific category

N = Number of patients in the ITT Population

CI = Confidence interval

Odds ratio, 95% CI, and p-value were obtained from the CMH tests controlling for geographic region, comparing linaclotide versus placebo.

The p-value met the criterion for statistical significance based on the multiple comparison procedure.

The percentage of 9/12 week Abdominal Pain Responders in the linaclotide group was 38.9% (156 patients) compared with 19.6% (79 patients) in the placebo group, with an odds ratio of 2.62 ($p < 0.0001$).

Sensitivity Analyses

Per request, the sponsor performed sensitivity analyses of 9/12 week abdominal pain and CSBM (APC) 3 + 1 responder. See Table 10

Table 10: 9/12 Week Abdominal Pain and CSBM (APC) 3+1 Responders Study MCP-103-302

Analysis	PLA	LIN	Diff (RFX-PLA)	P-value
(LOCF)	18/403 (4.5%)	68/401 (17.0%)	12.5%	<0.0001
Completed Case	11/245 (4.5%)	47/253 (18.6%)	14.1%	<0.0001
Observed Case	12/400 (3.0%)	51/394 (12.9%)	9.9%	<0.0001
Worst Case 1	11/403 (2.7%)	47/401 (11.7%)	9.0%	<0.0001
Worst Case 2	169/403 (41.9%)	47/401 (11.7%)	-30.2%	<0.00001
Worst Case 3	58/403 (14.4%)	51/401 (11.7%)	-1.7%	0.5056
Multiple Imputation	3.5%	16.4%	12.9%	<0.0001

Compiled from Tables 14.4.1.1D-14.4.1.1.I and 14.4.1.1k

P- values were obtained from the CMH tests controlling for geographic region.

The complete case analysis includes only those patients who complete at least 4 IVRS calls for each of the first 12 weeks of treatment.

The observed case analysis includes only those patients who complete at least 4 IVRS calls for at least one of the first 12 weeks of treatment.

For worst case analysis 1, patients must complete at least 4 IVARS calls for each of the first 12 weeks of treatment.

For worst case analysis 2, patients who do not complete at least 4 IVRS call for each of the first 12 weeks of treatment are handled as follows: patients randomized to Linaclotide are non-responders, while patients who are randomized to placebo are considered responders.

For worst case analysis 3, for those weeks where patients do not complete at least 4 IVRS calls, patients randomized to Linaclotide are non-responders, while patients who are randomized to placebo are considered responders.

Medical Officer's Comment:

The sponsor's worst case 1 analysis is more conservative than the sponsor's LOCF or OC analysis, however it remains statistically significant.

Table 11: Primary Efficacy Analysis: 9/12 Week Abdominal Pain Responders (ITT Population)

Description	Placebo (N=403) n (%)	Linaclotide (N=401) n (%)
Responder	79 (19.6)	156 (38.9)
Non-Responder	324 (80.4)	245 (61.1)
Difference in Responder Rate (Linaclotide - Placebo)	19.3	
Odds Ratio for Response (Linaclotide : Placebo)	2.62	
95% CI for Odds Ratio	(1.91, 3.60)	
p-value	< 0.0001	

A 9/12 week Abdominal Pain Responder was a patient who met the weekly Abdominal Pain Responder criteria for at least 9 of the first 12 weeks of the Treatment Period.

n = Number of patients within a specific category

N = Number of patients in the ITT Population

CI = Confidence interval

Odds ratio, 95% CI, and p-value were obtained from the CMH tests controlling for geographic region, comparing linaclotide versus placebo.

The p-value met the criterion for statistical significance based on the multiple comparison procedure.

The percentage of 9/12 week CSBM 3+1 Responders in the linaclotide group was 18% (72 patients) compared with 5% (20 patients) in the placebo group, with an odds ratio of 4.19 (p < 0.0001).

Table 12: Primary Efficacy Analysis: 9/12 Week CSBM 3+1 Responders (ITT Population)

Description	Placebo (N=403) n (%)	Linaclotide (N=401) n (%)
Responder	20 (5.0)	72 (18.0)
Non-Responder	3830(95.0)	3290(82.0)
Difference in Responder Rate (Linaclotide - Placebo)	13	
Odds Ratio for Response (Linaclotide : Placebo)	4.19	
95% CI for Odds Ratio	(2.50, 7.03)	
p-value	< 0.0001	

A 9/12 week CSBM 3+1 responder was a patient who met the weekly CSBM 3+1 responder criteria for at least 9 of the first 12 weeks of the Treatment Period.

n = Number of patients within a specific category

N = Number of patients in the ITT Population

CI = Confidence interval

Odds ratio, 95% CI, and p-value were obtained from the CMH tests controlling for geographic region, comparing linaclotide versus placebo.

The p-value met the criterion for statistical significance based on the multiple comparison procedure.

The percentage of 6/12 week APC +1 Responders was 33.7% (135 patients) in the linaclotide group compared with 13.9% (56 patients) in the placebo group, with an odds ratio of 3.16 (p < 0.0001).

Table 13: Primary Efficacy Analysis: 6/12 Week APC +1 Responders (ITT Population)

Description	Placebo (N=403) n (%)	Linaclotide (N=401) n (%)
Responder	56 (13.9)	135 (33.7)
Non-Responder	347 (86.1)	266 (66.3)
Difference in Responder Rate (Linaclotide - Placebo)	19.8	
Odds Ratio for Response (Linaclotide : Placebo)	3.16	
95% CI for Odds Ratio	(2.22, 4.49)	
p-value	< 0.0001	

A 6/12 week APC +1 Responder was a patient who met the weekly APC +1 Responder criteria for at least 6 of the first 12 weeks of the Treatment Period.

n = Number of patients within a specific category

N = Number of patients in the ITT Population

CI = Confidence interval

Odds ratio, 95% CI, and p-value were obtained from the CMH tests controlling for geographic region, comparing linaclotide versus placebo.

The p-value met the criterion for statistical significance based on the multiple comparison procedure

Exploratory Analysis of Primary Endpoints

Medical officer's Comments:

As seen from Table 14 and Table 15 (next page), weekly analysis shows statistically significant results in favor of linaclotide at almost every week during the course of the 26-week study in the linaclotide group compared with subjects in the placebo group. Similar results were obtained for analysis of the Weekly Abdominal Pain and CSBM (APC) +1 Responder Analysis, and the monthly responder analysis was also statically significant for both endpoints. See also statistical review by Milton Fan, PhD.

Table 14: Weekly Abdominal Pain and CSBM (APC) 3 + 1 Responder Rate by Treatment Group - Intention-to-Treat Population

Study MCP-103-302				
	PLA	LIN	Diff (LIN-PLA)	Chi-square p-value
Week 1	16/403 (4.0%)	51/401 (12.7%)	8.7%	<0.0001
Week 2	20/403 (5.0%)	81/401 (20.2%)	15.2%	<0.0001
Week 3	33/403 (8.2%)	88/401 (21.9%)	13.7%	<0.0001
Week 4	31/403 (7.7%)	95/401 (23.7%)	16.0%	<0.0001
Week 5	37/403 (9.2%)	92/401 (22.9%)	13.7%	<0.0001
Week 6	33/403 (8.2%)	97/401 (24.2%)	16.0%	<0.0001
Week 7	36/403 (8.9%)	95/401 (23.7%)	14.8%	<0.0001
Week 8	27/403 (6.7%)	103/401 (25.7%)	19.0%	<0.0001
Week 9	33/403 (8.2%)	85/401 (21.2%)	13.0%	<0.0001
Week 10	40/403 (9.9%)	89/401 (22.2%)	12.3%	<0.0001
Week 11	33/403 (8.2%)	86/401 (21.4%)	13.2%	<0.0001
Week 12	40/403 (9.9%)	103/401 (25.7%)	15.8%	<0.0001
Week 13	38/403 (9.4%)	6/401 (23.9%)	14.5%	<0.0001
Week 14	35/403 (8.7%)	97/401 (24.2%)	15.5%	<0.0001
Week 15	36/403 (8.9%)	86/401 (21.4%)	12.5%	<0.0001
Week 16	35/403 (8.7%)	92/401 (22.9%)	14.2%	<0.0001
Week 17	41/403 (10.2%)	92/401 (22.9%)	12.7%	<0.0001
Week 18	38/403 (9.4%)	87/401 (21.7%)	12.3%	<0.0001
Week 19	43/403 (10.7%)	92/401 (22.9%)	12.2%	<0.0001
Week 20	36/403 (8.9%)	83/401 (20.7%)	11.8%	<0.0001
Week 21	33/403 (8.2%)	88/401 (21.9%)	13.7%	<0.0001
Week 22	32/403 (7.9%)	95/401 (23.7%)	15.8%	<0.0001
Week 23	36/403 (8.9%)	86/401 (21.4%)	12.5%	<0.0001
Week 24	40/403 (9.9%)	82/401 (20.4%)	10.5%	<0.0001
Week 25	37/403 (9.2%)	91/401 (22.7%)	13.5%	<0.0001
Week 26	27/403 (6.7%)	79/401 (19.7%)	13.0%	<0.0001

Table 15: Monthly Abdominal Pain and CSBM (APC) 3 + 1 Responder Rate by Treatment Group

Study MCP-103-302				
	PLA	LIN	Diff (LIN-PLA)	Chi-square p-value
Month 1	28/403 (6.9%)	97/401 (24.2%)	17.2%	<0.0001
Month 2	35/403 (8.7%)	115/401 (28.7%)	20.0%	<0.0001
Month 3	43/403 (10.7%)	107/401 (26.7%)	16.0%	<0.0001
Month 4	41/403 (10.2%)	100/403 (24.9%)	14.7%	<0.0001
Month 5	47/403 (11.7%)	98/401 (24.4%)	12.7%	<0.0001
Month 6	40/403 (9.9%)	99/401 (24.7%)	14.8%	<0.0001

Compiled by Milton Fan, PhD from Table 14.4.3.24C.

P-values were obtained by the CMH tests controlling for geographic region.

5.3.1.8 Analysis of Secondary Endpoints(s)

Medical Officer's Comments:

While the majority of the secondary endpoints reach statistically significant p-values, many of the endpoints (e.g., straining, bloating and abdominal discomfort) are poorly defined, not validated and may not be clinically meaningful.

There were 10 secondary efficacy parameters (8 change-from-baseline parameters and 2 responder parameters). All change-from-baseline parameters were based on the first 12-weeks of the Treatment Period.

For each of the 8 change-from-baseline parameters, the linaclotide group was compared with the placebo group using an analysis of covariance (ANCOVA) model with treatment group and geographic region as fixed-effect terms and the corresponding baseline value as a covariate. Least squares mean change from baseline for each treatment group, difference in least squares mean change between the linaclotide and placebo group, the corresponding confidence interval, and the 2-sided p-value associated with the between-group comparison were reported.

For each of the 2 responder parameters, the proportion of responders in the linaclotide group was compared with the proportion in the placebo group using a CMH test controlling for geographic region. The number and percentage of responders in each treatment group, the difference in responder rate between the linaclotide and placebo group, the odds ratio and the corresponding confidence interval (CI), and the 2 sided p value associated with the CMH tests are presented in Table 16, on page 60.

Table 16: Overview of Secondary Efficacy Parameter Results (ITT Population)

Secondary Efficacy Parameters			
Parameter	Mean Baseline	LS Mean Change from Baseline (SE)	
Stool Consistency (BSFS Score)	2.3	0.6 (0.1)	1.9 (0.1) ^b
SBMs/Week	1.7	1.3 (0.2)	4.0 (0.2) ^b
Straining (5-point ordinal scale)	3.6	-0.7 (0.0)	-1.2 (0.0) ^b
CSBMs/Week	0.2	0.7 (0.1)	2.2 (0.1) ^b
Bloating (11-point NRS scale)	6.6	-1.0 (0.1)	-1.9 (0.1) ^b
Abdominal Discomfort (11-point NRS scale)	6.1	-1.1 (0.1)	-1.9 (0.1) ^b
Abdominal Pain (11-point NRS scale)	5.6	-1.1 (0.1)	-1.9 (0.1) ^b
6/12 Week CSBM +1 Responder			
Responder, n (%)	--	91 (22.6)	191 (47.6) ^a
Odds Ratio (95% CI)	--		3.1 (2.3, 4.2)
6/12 Week Abdominal Pain Responder			
Responder, n (%)	--	139 (34.5)	196 (48.9) ^a
Odds Ratio (95% CI)	--		1.8 (1.4, 2.4)
Abdominal Pain-free Days ^c	2.1	-0.1 (0.0)	0.1 (0.0) ^b

a. p-values based on the CMH test controlling for geographic region; $p < 0.0001$. All p-values met the criteria for statistical significance based on the MCP.

b. p-values based on a comparison of linaclotide versus placebo in an ANCOVA model with treatment group and geographic region as factors and baseline value as covariate; $p < 0.0001$ for all parameters except abdominal pain-free days ($p = 0.0003$). All p-values met the criteria for statistical significance based on the MCP.

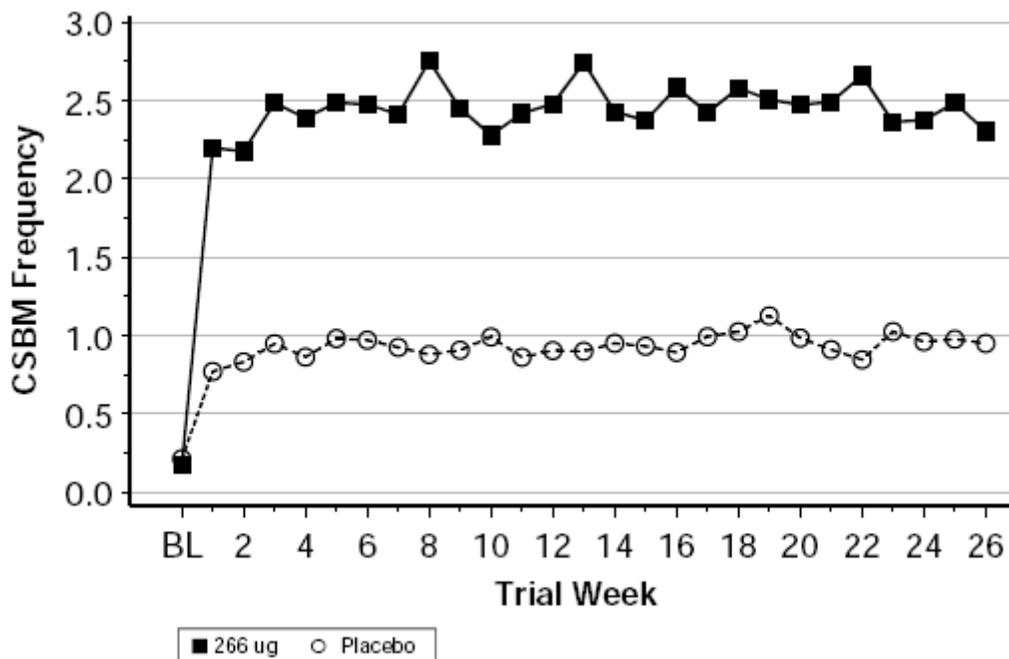
c. LS mean change from baseline and p-values based on rank-transformed normal scores.

1) Change from Baseline in 12-week CSBM Frequency Rate (See Figure 5 on page 61)

A patient's 12-week CSBM frequency rate was the CSBM rate (CSBMs/week) calculated over the first 12 weeks of the Treatment Period.

The mean baseline values for CSBM frequency rates were low in both treatment groups (0.21 per week for patients in the placebo group and 0.18 per week for patients in the linaclotide group). Following 12 weeks of treatment with linaclotide at a dose of 266 ug, the least squares (LS) mean change from baseline in CSBM frequency rate was 2.24 CSBMs per week; in comparison, the LS mean change from baseline in the placebo group was 0.70 CSBMs per week. This difference between treatment groups was statistically significant at a p-value of < 0.0001 .

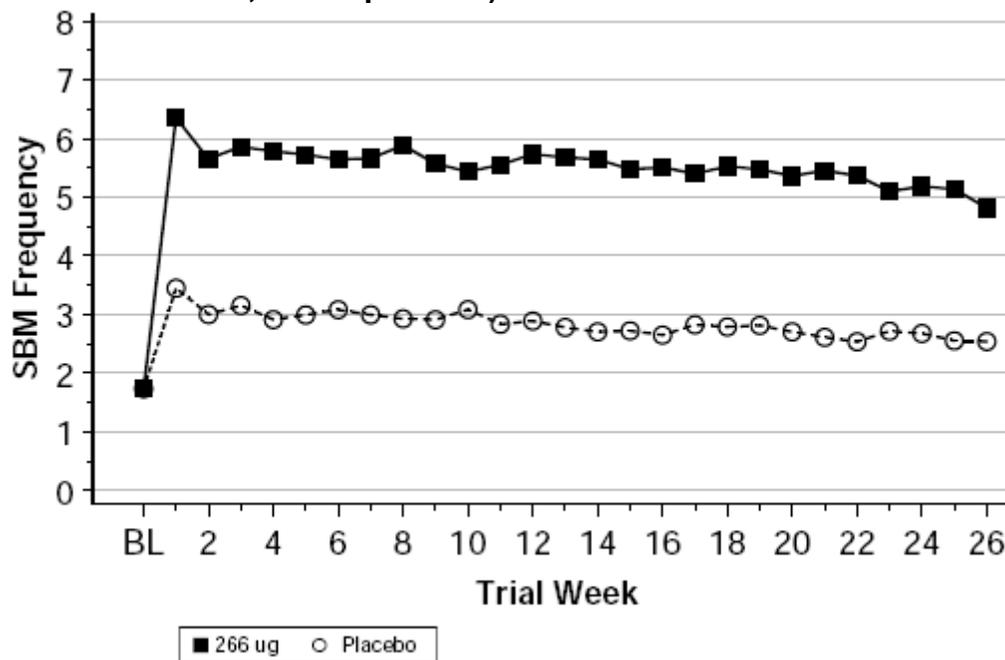
Figure 5: Mean CSBM Frequency Rate during Each Week of the Treatment Period (Observed Cases; ITT Population)



- 2) Change from Baseline in 12-week SBM Frequency Rate (see Figure 6 on page 62)
A patient's 12-week SBM frequency rate was the SBM rate (SBMs/week) calculated over the first 12 weeks of the Treatment Period.

The mean baseline values for SBM frequency rates were similar between treatment groups (1.74 per week for patients in the placebo group and 1.75 per week for patients in the linaclotide group). Following 12 weeks of treatment with linaclotide at a dose of 266 ug, the LS mean change from baseline in SBM frequency rate was 4.02 SBMs per week; in comparison, the LS mean change from baseline in the placebo group was 1.31 SBMs per week. This difference between treatment groups was statistically significant ($p < 0.0001$).

Figure 6: Mean SBM Frequency Rate during Each Week of the Treatment Period (Observed Cases; ITT Population)



3) Change from Baseline in 12-week Stool Consistency

Stool consistency was measured for each BM using the 7-point BSFS scale. The patient's 12-week Stool Consistency score was the average of the non-missing BSFS scores from the SBMs reported by the patient during the first 12 weeks of the Treatment Period.

Patients had an average baseline BSFS score of 2.3 in the placebo group and 2.4 in the linaclotide group, which is indicative of a hard, lumpy, cracked stool form. The difference between linaclotide and placebo in change from baseline in 12-week stool consistency was statistically significant, with LS mean changes from baseline of 1.91 and 0.61 in the linaclotide and placebo groups, respectively ($p < 0.0001$).

4) Change from Baseline in 12-week Severity of Straining

Severity of straining was measured for each BM using a 5-point ordinal scale. The patient's 12-week Severity of Straining score was the average of the non-missing Severity of Straining scores from the SBMs reported by the patient during the first 12 weeks of the Treatment Period.

Patients in the linaclotide group had a decrease in straining from 3.570 (moderate straining) at baseline to 2.295 (a little bit of straining) for Weeks 1-12. The placebo group had a less robust decrease in straining, from 3.545 at baseline to 2.854. The difference between linaclotide and placebo in change from baseline in 12-week straining was statistically significant ($p < 0.0001$).

5) Change from Baseline in 12-week Abdominal Pain

Patients were asked daily to rate the severity of their Abdominal Pain at its Worst over the last 24 hours using an 11-point NRS. A patient's 12-week Abdominal Pain score was the average of the non-missing daily patient assessments of Abdominal Pain at its Worst reported during the first 12 weeks of the Treatment Period.

The placebo group had a LS mean decrease in worst pain of 1.070 points, compared with a decrease of 1.852 points in the linaclotide group. The difference between linaclotide and placebo in change from baseline in 12-week abdominal pain was statistically significant ($p < 0.0001$).

6) Change from Baseline in 12-week Abdominal Discomfort

Abdominal Discomfort was measured daily using an 11-point NRS. The patient's 12-week Abdominal Discomfort score was the average of the non-missing daily patient assessments of Abdominal Discomfort reported during the first 12 weeks of the Treatment Period.

The placebo group had a LS mean decrease in discomfort of 1.103 points, compared with a decrease of 1.940 points in the linaclotide group. The difference between linaclotide and placebo in change from baseline in 12-week abdominal discomfort was statistically significant ($p < 0.0001$).

7) Change from Baseline in 12-week Bloating

Bloating was measured daily using an 11-point NRS. The patient's 12-week Bloating score was the average of the non-missing daily patient assessments of bloating scores reported during the first 12 weeks of the Treatment Period.

The placebo group had a LS mean decrease in discomfort of 1.032 points, compared with a decrease of 1.914 points in the linaclotide group. The difference between linaclotide and placebo in change from baseline in 12-week bloating was statistically significant ($p < 0.0001$).

8) 6/12 Week CSBM +1 Responder

A 6/12 Week CSBM +1 Responder was a patient who meets the Weekly CSBM +1 Responder criteria for at least 6 out of the first 12 weeks of the Treatment Period.

The percentage of responders in the linaclotide group was significantly greater than in the placebo group (47.6% and 22.6%, respectively; $p < 0.0001$).

9) 6/12 Week Abdominal Pain Responder

A 6/12 Week Abdominal Pain Responder was a patient who met the Weekly Abdominal Pain Responder criteria for at least 6 out of the first 12 weeks of the Treatment Period.

The percentage of responders in the linaclotide group was significantly greater than in the placebo group (48.9% and 34.5%, respectively; $p < 0.0001$).

10) Change from Baseline in 12-week Percent of Abdominal Pain-free Days

Patients were asked daily to rate their Abdominal Pain at its Worst over the last 24 hours using an 11-point NRS. Abdominal Pain-Free Days were those days on which the patient reported a score of 0 for the severity of his or her abdominal pain at its worst over the last 24 hours. A patient's 12-week Percent of Abdominal Pain-Free Days was calculated as the number of Abdominal Pain-Free Days during the first 12 weeks of the Treatment Period divided by the total number of days with non-missing daily abdominal pain at its worst assessments during the first 12 weeks of the Treatment Period multiplied by 100.

The mean percent of abdominal pain-free days increased by 4.83% in the placebo group and by 10.49% in the linaclotide group during the Treatment Period. The difference between linaclotide and placebo in change from baseline in 12-week percent of abdominal pain-free days (rank-transformed normal scores) was statistically significant ($p = 0.0003$).

5.3.1.9 Other Endpoints

Medical Officer's Comments:

These other endpoints are exploratory, poorly defined and not validated, as such the clinical meaningfulness is questionable.

Changes from baseline in the IBS-Symptom Severity Score (IBS-SSS) during the Treatment Period were analyzed. Scores for each of the 5 assessments could range from 0 to 100, with lower scores representing a more favorable condition; the total score, which was the sum of the 5 individual scores, could vary from 0 to 500. The linaclotide group showed a greater improvement from baseline to Weeks 12 and 26 in all components of the IBS-SSS compared with the placebo group ($p < 0.0001$).

More patients in the linaclotide group were satisfied with the treatment they received compared with patients in the placebo group, when queried at each study visit about the medication's ability to relieve IBS-C symptoms. Similarly, when queried at the end of the Treatment Period, more linaclotide patients than placebo patients indicated that they would consider continuing the study medication if given the option.

The improvement in quality of life at Week 12 and at Week 26 (End of the Treatment Period) was demonstrated overall and for each of the 8 subscale scores in patients treated with linaclotide, as compared with patients treated with placebo ($p \leq 0.0358$).

5.3.1.10 Subpopulations

Table 17: Subgroup Analyses of Proportion of 9/12 Week Abdominal Pain and CSBM (APC) 3+1 Responders Study MCP-103-302

Subgroup	Placebo	Linaclotide (LIN-PLA)		95% CI
Gender				
Male	3/51 (5.9%)	5/33 (15.2%)	9.3%	(8.8%, 9.7%)
Female	9/352 (2.6%)	46/368 (12.5%)	9.9%	(9.8%, 10.1%)
Age				
<65	12/386 (3.1%)	47/378 (12.4%)	9.3%	(9.2%, 9.4%)
≥65	0/17 (0.0%)	4/23 (17.4%)	17.4%	(16.9%, 17.9%)
Race				
White	9/311 (2.9%)	43/316 (13.6%)	10.7%	(10.6%, 10.8%)
Black	2/78 (2.6%)	7/70 (10.0%)	7.4%	(7.2%, 7.7%)
Other	1/14 (7.1%)	1/15 (6.7%)	-0.4%	(-1.1%, 0.1%)
BMI at baseline				
< 30 kg/m ²	7/285 (2.5%)	35/280 (12.5%)	10.0%	(9.9%, 10.2%)
≥ 30 kg/m ²	5/118 (4.2%)	16/121 (13.2%)	9.0%	(8.8%, 9.2%)
Abdominal Pain at Baseline				
< 5	4/176 (2.3%)	21/165 (12.7%)	10.4%	(10.3%, 10.6%)
≥ 5 < 8	7/185 (3.8%)	27/189 (14.3%)	10.5%	(10.3%, 10.7%)
≥ 8	1/42 (2.4%)	3/47 (6.4%)	4.0%	(-3.7%, 4.3%)

Compiled by Milton fan, PhD from Table 14.4.1.1J

Medical Officer's Comment:

This subgroup responder analysis shows efficacy in a higher proportion of patients greater than 65 years of age, white race, and those with abdominal pain less than 8 at baseline, and a slight increase in females and those with baseline BMI < 30 kg/m². However, all these subgroups are small and the differences in treatment response are not statistically significant secondary to the small numbers.

5.3.1.11 Analysis of Clinical Information Relevant to Dosing Recommendations

See discussion in Section

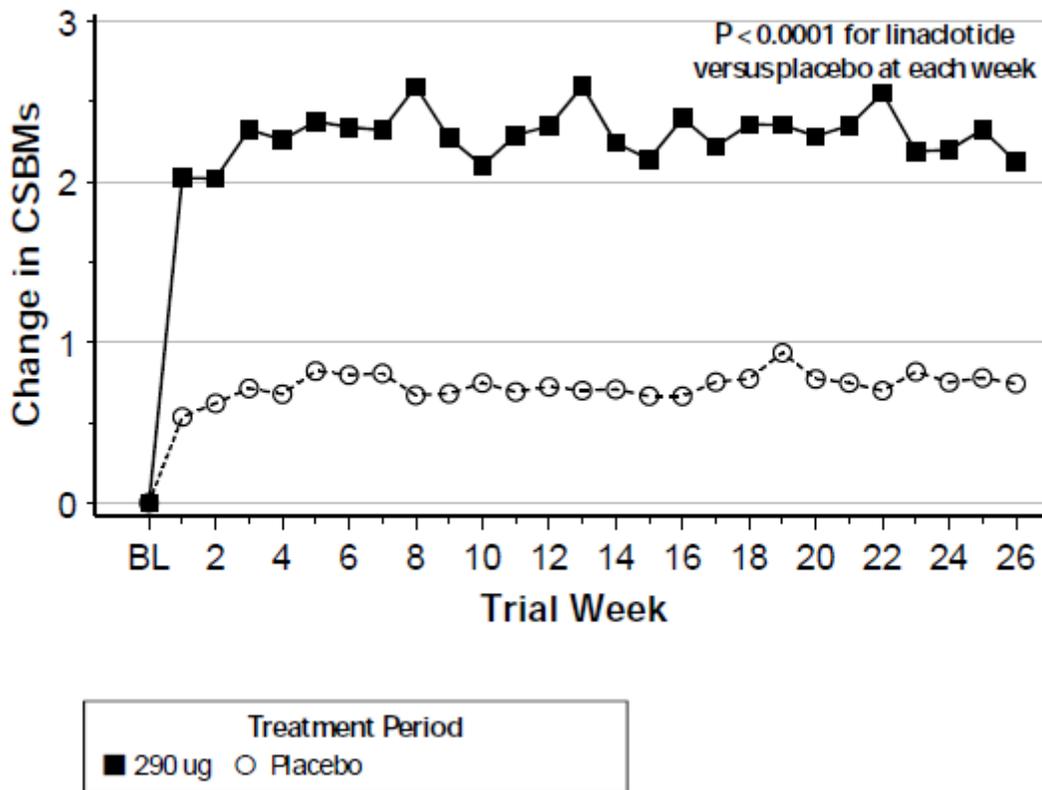
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations on page 108 for discussion of dosing and dose ranging trials.

5.3.1.12 Discussion of Persistence of Efficacy and/or Tolerance Effects

Medical Officers Comments:

Other than CSBM rate and abdominal pain, the other endpoints analysed below are exploratory and not validated. Therefore conclusions as to the clinical meaningfulness of these endpoints to patients' cannot be reached.

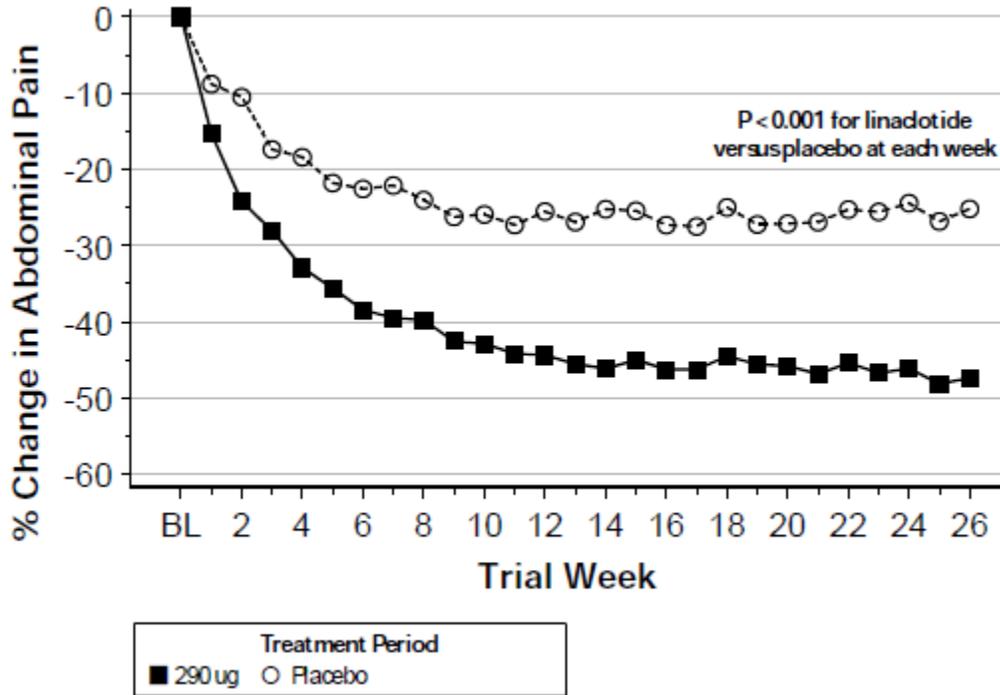
Figure 7: LS Mean Changes from Baseline in CSBM Frequency Rate by Week Over 26 Weeks (MCP-103-302) ITT Population



p-values are based on a comparison of linaclotide versus placebo in an ANCOVA model with treatment group, trial, and geographic region as factors and baseline value as covariate

For Abdominal Pain linaclotide showed improvements over placebo at each week ($p < 0.0001$). Additionally, the results of MCP-103-302 show that linaclotide 290 ug improved these abdominal symptoms from Week 12 through Week 26. See Figure 8.

Figure 8: Percent Change from Baseline in Abdominal Pain at its Worst by Week Over 26 Weeks (MCP-103-302 ITT Population)



p-values are based on a comparison of linaclotide versus placebo in an ANCOVA model with treatment group, trial, and geographic region as factors and baseline value as covariate

See discussion in Section 5.3.2.12 Discussion of Persistence of Efficacy and/or Tolerance Effects on page 86, for discussion of Trial LIN-MD-31 with randomized withdrawal protocol.

5.3.1.13 Additional Efficacy Issues/Analyses

The results of these sensitivity analyses indicate that there was no meaningful impact of the duplicate patients on the primary efficacy results for trial MCP-103-302. See discussion in Table 18.

Table 18: Results of Duplicate-patient Sensitivity Analysis for the Primary Efficacy Parameters for MCP-103-302 (ITT Population)

Parameter		Primary Analysis N = 804	Excluding All Duplicate-Patient Data N = 798	Including All Duplicate-Patient Data ^a
9/12 Week APC 3 + 1 Responder	Placebo n/N (%)	12/403 (3.0)	11/400 (2.8)	-
	Linaclotide n/N (%)	51/401 (12.7)	50/398 (12.6)	-
	p-value	< 0.0001	< 0.0001	-
9/12 Week CSBM 3 + 1 Responder	Placebo n/N (%)	20/403 (5.0)	19/400 (4.8)	-
	Linaclotide n/N (%)	72/401 (18.0)	71/398 (17.8)	-
	p-value	< 0.0001	< 0.0001	-
9/12 Week Abdominal Pain Responder	Placebo n/N (%)	79/403 (19.6)	76/400 (19.0)	-
	Linaclotide n/N (%)	156/401 (38.9)	155/398 (38.9)	-
	p-value	< 0.0001	< 0.0001	-
6/12 Week APC +1 Responder	Placebo n/N (%)	56/403 (13.9)	54/400 (13.5)	-
	Linaclotide n/N (%)	135/401 (33.7)	134/398 (33.7)	-
	p-value	< 0.0001	< 0.0001	-

Refer to Section 3.2.1.3 for definitions of the Responder parameters. p-value based on the CMH test controlling for geographic region.

a. For Trial MCP-103-302, no patient was randomized multiple times, as such the sensitivity analysis of including all duplicate patient data is equivalent to the primary analysis.

5.3.2 LIN-MD-31 - Evaluation of Efficacy and Safety of Multiple Doses of Linaclotide

Medical Officer's Comments:

See discussion in Section 6 Review of Efficacy on page 93 for Summary of this trial data.

Note: during the course of development the analytical procedures for determining the linaclotide content have been optimized resulting in changes of the expression of the dose but not the actual dose strength of the capsules. Thus in LIN-MD-31 the dose strength was expressed as 300ug, subsequently this was updated to an expressed dose of 266ug. After completion of the trial the finalized dose expression is 290ug.

5.3.2.1 Indication

The objective of this trial was to determine the efficacy and safety of linaclotide administered to patients with IBS-C.

5.3.2.2 Methods

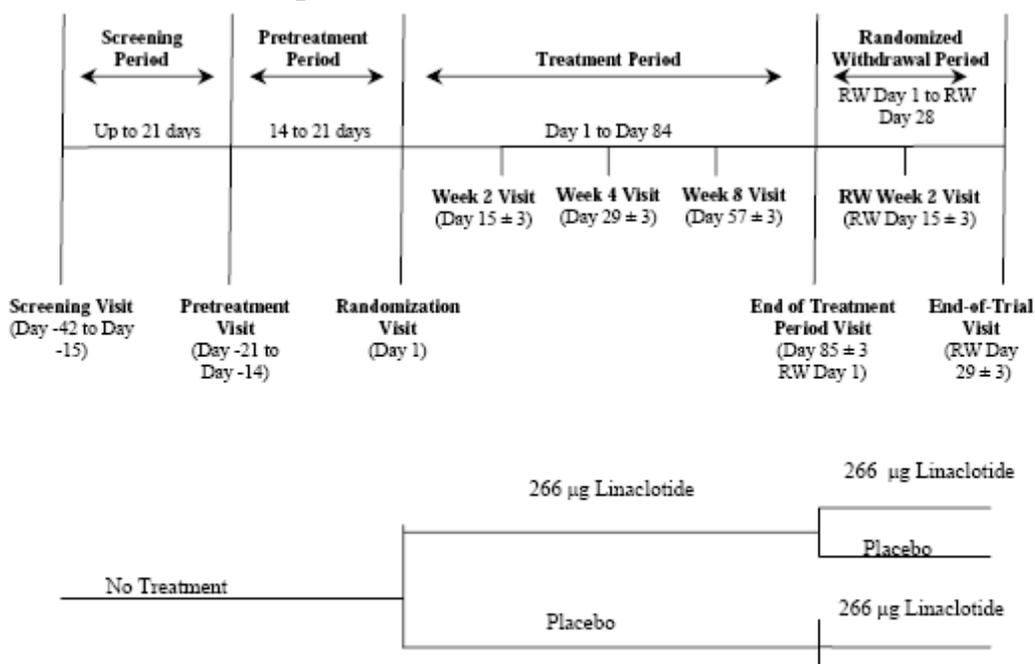
This clinical study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial comparing one dose (266µg) of linaclotide with placebo. A total of 118 trial centers enrolled patients, and 803 patients with a diagnosis of IBS-C (modified Rome II criteria) were randomized.

The trial consisted of up to 21 days of screening, 14 to 21 days of pretreatment, and 12 weeks of double-blind treatment. At the end of the pretreatment period, during which patients provided qualifying bowel habits, symptom severity, and rescue medicine information, patients meeting the entry criteria for this trial were randomized to 1 of 2 double-blind treatment groups: 266µg linaclotide or placebo (1:1).

Patients who complete the 12-week treatment period were eligible to enter the 4-week randomized withdrawal (RW) period and, in a double-blind manner, were allocated study drug as follows:

- Patients randomized to 266 µg linaclotide during the treatment period were re-randomized to 266 µg linaclotide or placebo (1:1).
- Patients randomized to placebo during the treatment period were assigned to receive 266 µg linaclotide.

Figure 9: Overview of Trial Design LIN-MD-31



Note: there is no Day 0.
 RW= Randomized Withdrawal

5.3.2.3 Population

Males and females aged 18 years and older were included if they met the following criteria:

- Patient reported abdominal discomfort or pain that had two or more of the following three features for at least 12 weeks, which need not be consecutive, in the 12 months before the Screening Visit (Visit 1) or before starting chronic treatment with tegaserod or lubiprostone:
 - (1) Relieved with defecation;
 - (2) Onset associated with a change in frequency of stool;
 - (3) Onset associated with a change in form (appearance) of stool.
- Patient reported < 3 bowel movements (BMs) per week, with each BM occurring in the absence of laxative/enema/suppository use during the preceding 24 hours and had 1 or more of the following symptoms for at least 12 weeks, which need not be consecutive, in the preceding 12 months:
 - (1) Straining during > 25% of BMs;
 - (2) Lumpy or hard stools during > 25% of BMs; and
 - (3) Sensation of incomplete evacuation during > 25% of BMs.

- Patient had an average score ≥ 3.0 for abdominal pain at its worst as reported in the IVRS using an 11-point numerical rating scale (NRS) during the 14 calendar days before the start of the treatment period.

In addition, patients had to report an average of < 3 complete spontaneous BMs (CSBMs) per week and 5 or fewer spontaneous BMs (SBMs) per week by the IVRS during the 14 days before the start of the treatment period, and be compliant with IVRS completion by adequately responding to IVRS questions on 10 or more of the 14 days before the start of the treatment period. An SBM was defined as a BM that occurred in the absence of laxative, enema, or suppository use on either the calendar day of the BM or the calendar day before the BM. A CSBM was defined as an SBM that was associated with a sense of complete evacuation.

Patients were excluded for any of the following reasons:

- (1) They reported loose (mushy) stools for $> 25\%$ of their BMs during the 12 weeks before the Screening Visit;
- (2) 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;
- (3) 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., before the Randomization Visit).

Exclusion and Inclusion criteria were otherwise the same as in trial MCP-103-302, See discussion in Section 5.3.1.2 Methods on page 40.

Number of Patients

A total of 803 patients were randomized, and 802 of them were included in the Safety Population; 800 of these patients were included in the Intent-to-Treat Population.

5.3.2.4 Subject Disposition

Overall, 803 patients (represented by 805 PIDs) were randomized to treatment; two patients were randomized at more than 1 study center but were only counted once. A total of 802 patients received double-blind study drug and were included in the Safety Population, and 800 patients had at least 1 post randomization entry of the primary efficacy assessment and were included in the ITT Population. A total of 647 patients entered the RW period of the study, 645 of whom received at least 1 dose of study drug and were included in the RW Population.

Table 19: Patient Populations

Patients screened = 2424			
Screen failures = 466			
Pretreatment failures = 1155			
	Placebo	Linaclotide	Total
Patients randomized	397	406	803
Safety Population	396	406	802
Intent-to-Treat Population	395	405	800
Entered RW period	335	312	647

RW = randomized withdrawal

5.3.2.5 Demographics

Overall, the mean patient age was 43.5 years and 90.5% of patients were female; most patients were Caucasian (76.9%) and non-Hispanic (85.9%). There were no meaningful differences between treatment groups, although the mean weight of the patients treated with linaclotide was higher than the mean weight of the patients treated with placebo (77.2 kg vs. 74.6 kg; $p = 0.0375$). The demographic data for the ITT Population were similar. See Table 20.

Table 20: Demographic and Baseline Characteristics—Safety Population

Characteristic	Placebo (N = 396)	Linacotide (N = 406)	Total (N = 802)	P-value
Age, years				
Mean ± SD	43.7 ± 12.9	43.3 ± 12.7	43.5 ± 12.8	0.6528
≥ 65 years, n (%)	26 (6.6)	19 (4.7)	45 (5.6)	0.3832
Range	18, 84	19, 81	18, 84	
Sex, n (%)				
Male	38 (9.6)	38 (9.4)	76 (9.5)	0.9295
Female	358 (90.4)	368 (90.6)	726 (90.5)	
Race, n (%)				
Caucasian	302 (76.3)	315 (77.6)	617 (76.9)	0.6391
Non-Caucasian	94 (23.7)	91 (22.4)	185 (23.1)	
Ethnicity, n (%)				
Hispanic	57 (14.4)	56 (13.8)	113 (14.1)	0.8354
Non-Hispanic	339 (85.6)	350 (86.2)	689 (85.9)	
Weight, kg				
Mean ± SD	74.6 ± 18.3	77.2 ± 18.8	75.9 ± 18.6	0.0375
Height, cm				
Mean ± SD	164.3 ± 8.3	165.2 ± 8.3	164.7 ± 8.3	0.1186
BMI, kg/m ²				
Mean ± SD	27.6 ± 6.2	28.3 ± 6.4	27.9 ± 6.3	0.1172

BMI = body mass index.

P-values for continuous variables (e.g., age, weight, height, BMI) were from an ANOVA with treatment group and geographic region as factors; p-values for categorical variables (e.g., sex, ethnicity, and race) were from a CMH test controlling for geographic region.

Almost all patients (about 96%) had a condition reported in at least 1 SOC. The most common disorders (≥ 15%) were hemorrhoids (27.6%), gastroesophageal reflux disease (21.7%), drug hypersensitivity (19.6%), insomnia (18.3%), headache (17.2%), seasonal allergy (17.1%), hypertension (17.0%), depression (16.8%), and anxiety (16.0%). A total of 100 patients (13.8% of female patients) were reported as postmenopausal and 183 (25.2%) had undergone a hysterectomy. There were no meaningful differences in medical and surgical history between the treatment groups.

The p-values for the differences in the Bristol Stool Form Scale (BSFS) and straining scores were significantly different, $p < 0.05$. The patients treated with linacotide had lower mean BSFS scores and higher mean straining scores at baseline relative to patients treated with placebo. There were no significant differences in the treatment groups in the other variables. See Table 21.

Drug Exposure

In the 12-week trial, the mean treatment duration was 75.0 days for the 290-ug dose, and 78.8 days for placebo.

Table 21: Efficacy Variables at Baseline—ITT Population

Parameter	Placebo (N = 395) Mean ± SD	Linaclotide (N = 405) Mean ± SD	P-value
CSBM rate per week	0.24 ± 0.50	0.20 ± 0.46	0.3149
SBM rate per week	1.90 ± 1.40	1.94 ± 1.38	0.6937
BSFS	2.41 ± 1.03	2.26 ± 1.00	0.0463
Straining score	3.43 ± 0.81	3.57 ± 0.76	0.0196
Abdominal pain	5.63 ± 1.71	5.66 ± 1.65	0.8553
Abdominal pain-free days	1.69 ± 6.00	2.06 ± 6.48	0.3971
Abdominal discomfort score	6.04 ± 1.67	6.17 ± 1.60	0.2734
Bloating score	6.50 ± 1.89	6.71 ± 1.77	0.0996

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

BSFS = Bristol Stool Form Scale; CSBM = complete spontaneous bowel movement; ITT = intent-to-treat; SBM = spontaneous bowel movement

Prior and Concomitant Medications

The most commonly used concomitant medications were generally similar between the treatment groups.

Compliance

Mean compliance in each treatment group was greater than 90% throughout the study. Compliance rates (patients with ≥ 80% complete calls) were 73.2% for patients treated with placebo and 71.1% for patients treated with linaclotide.

5.3.2.6 Efficacy Assessments

Five populations were considered in the statistical analysis of the study.

Screened Population

The Screened Population consisted of all patients who had a Screening Visit (Visit 1) and were assigned a PID number

Randomized Population

The Randomized Population consisted of all patients in the Screened Population who were randomized to a treatment group at the Randomization Visit (Visit 3).

Safety Population

The Safety Population consisted of all patients in the Randomized Population who received at least 1 dose of double-blind study medication during the treatment period.

Intent-to-Treat Population

The Intent-to-Treat (ITT) Population consisted of all patients in the Safety Population who had at least 1 postrandomization entry of the primary efficacy assessment (i.e., the

assessment of abdominal pain at its worst or daily IVRS information that determined whether an SBM is a CSBM).

Randomized Withdrawal Population

The RW Population consisted of all patients who were rerandomized or assigned to treatment in the RW period and had at least 1 dose of double-blind study drug during the RW period. For the RW period, there were 3 treatment sequences as follows:

- **266 µg-266 µg** (266 µg linaclotide administered in the treatment period, followed by 266 µg linaclotide in the RW period)
- **266 µg-Placebo** (266 µg linaclotide administered in the treatment period, followed by placebo in the RW period)
- **Placebo-266 µg** (placebo administered in the treatment period, followed by 266 µg linaclotide in the RW period)

Excluded Patients

Two patients enrolled into the study at more than one study center. These patients were included in the analyses only under the first assigned PID.

The primary analysis and all secondary and additional analyses were performed on the ITT Population.

An OC approach was applied to missing post baseline data (i.e., a patient's missing values were not imputed). Any diminished treatment group sample sizes in the analyses represent missing observations for the calculated parameters. Additionally, if no SBM occurred for a patient for a given period, the corresponding SBM-dependent parameters could not be calculated. For example, 92 (11.5%) patients did not have an SBM during the pretreatment period, and therefore, these patients did not have a baseline straining or stool consistency score. In addition to the OC approach, an LOCF approach was used for sensitivity analyses for all secondary efficacy parameters that were defined on a weekly basis.

The overall family-wise error rate for testing the primary and secondary efficacy parameters was controlled at the 0.05 significance level using a 5-step serial gatekeeping MCP. Nominal p-values unadjusted for multiplicity are presented for all analyses. However, for each of the primary and secondary efficacy parameters, the result was considered statistically significant only if the corresponding MCP criteria were met. There were 4 primary efficacy parameters and 10 secondary efficacy parameters. After applying the prespecified MCP, the applicant reported all 14 comparisons were statistically significant.

Primary Efficacy Assessment

There were 2 primary efficacy assessments used to determine the primary efficacy parameters.

➤ **Daily Patient Assessment of Abdominal Pain at its Worst**

Patient assessment of abdominal pain at its worst was collected daily by IVRS calls. The rating was provided by the patient answering the following question:

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

➤ **Spontaneous Bowel Movement and Complete Spontaneous Bowel Movement**

SBM was defined as a BM that occurred in the absence of laxative, enema, or suppository use on either the calendar day of the BM or the calendar day before the BM. A CSBM was defined as an SBM that was associated with a sense of complete evacuation.

Secondary Efficacy Assessments

In addition to the primary efficacy assessments, the following efficacy assessments were used in determining the secondary efficacy parameters:

1. Daily Patient Assessment of Abdominal Discomfort – 11-point scale
2. Daily Patient Assessment of Bloating – 11-point scale
3. Stool Consistency (Bristol Stool Form Scale) - The 7-point ordinal BSFS
4. Severity of Straining – 5-point scale

Additional Efficacy Parameters

In addition to the primary and secondary efficacy assessments, the following efficacy assessments were used in determining the additional efficacy parameters:

1. Daily Patient Assessment of Abdominal Cramping – 11-point scale
2. Daily Patient Assessment of Abdominal Fullness – 11-point scale
3. Daily Patient Assessment of Per-Protocol Rescue Medicine or Any Other Laxative, Suppository, or Enema Use
4. Bowel Movement within 24 Hours of Receiving Study Drug – yes/no/how many
5. Unsuccessful Attempts to have a BM – yes/no/how many
6. Weekly Patient Assessment of Constipation Severity – 5-point scale
7. Weekly Patient Assessment of IBS Symptom Severity – 5-point scale
8. Weekly Patient Assessment of Degree of Relief of IBS Symptoms – 7-point scale
9. Weekly Patient Assessment of Adequate Relief of IBS Symptoms – yes/no
10. IBS-Symptom Severity Score Assessment – baseline and EOT
11. Treatment-Satisfaction Assessment – 5-point scale
12. Treatment-Continuation Assessment – 5-point scale

5.3.2.7 Analysis of Primary Endpoint(s)

There were 4 primary efficacy parameters:

- 9/12 week APC (abdominal pain and CSBM) 3+1 responder
This patient met the weekly APC 3+1 responder criteria for at least 9 out of the 12 weeks of the treatment period. For each week in the treatment period, a weekly APC 3+1 responder was a patient who had at least 3 CSBMs and an increase of at least 1 CSBM from baseline for that week, and also had a decrease of at least 30% in the mean abdominal pain score for that week. If a patient did not have a CSBM weekly rate or mean abdominal pain score, or had less than 4 complete IVRS calls for a particular treatment period week, the patient was not considered a responder for that week.
- 9/12 week CSBM 3+1 responder
This patient met the weekly CSBM 3+1 responder criteria for at least 9 out of the 12 weeks of the treatment period. For each week in the treatment period, a weekly CSBM 3+1 responder was a patient who had at least 3 CSBMs and an increase of at least 1 CSBM from baseline for that week. If a patient did not have a CSBM weekly rate or had less than 4 complete IVRS calls for a particular treatment period week, the patient was not considered a responder for that week.
- 9/12 week abdominal pain responder
This patient met the weekly abdominal pain responder criteria for at least 9 out of the 12 weeks of the treatment period. For each week in the treatment period, a weekly abdominal pain responder was a patient who had a decrease of at least 30% in the mean abdominal pain score from baseline for that week. If a patient did not have a mean abdominal pain score or had less than 4 complete IVRS calls for a particular treatment period week, the patient was not considered a responder for that week.
- 6/12 week APC 1+1 responder
This patient met the weekly APC 1+1 responder criteria for at least 6 out of the 12 weeks of the treatment period. For each week in the treatment period, a weekly APC 1+1 responder was a patient who had an increase of at least 1 CSBM from baseline for that week, and also had a decrease of at least 30% in the mean abdominal pain score for that week. If a patient did not have a CSBM weekly rate or mean abdominal pain score, or had less than 4 complete IVRS calls for a particular treatment period week, the patient was not considered a responder for that week.

Table 22: Overview of Primary Efficacy Parameters - ITT Population

Primary Efficacy Parameters				
Parameter	Placebo (N = 395) n (%)	Linaclotide (N = 405) n (%)	Statistics	
			Odds Ratio (95% CI)	P-value ^a (Significant by MCP)
9/12 Week APC 3+1 responder	20 (5.1)	49 (12.1)	2.60 (1.51, 4.47)	0.0004 (yes)
9/12 Week CSBM 3+1 responder	25 (6.3)	79 (19.5)	3.65 (2.26, 5.88)	< 0.0001 (yes)
9/12 Week abdominal pain responder	107 (27.1)	139 (34.3)	1.41 (1.04, 1.91)	0.0262 (yes)
6/12 Week APC +1 responder	83 (21.0)	136 (33.6)	1.93 (1.40, 2.66)	< 0.0001 (yes)

^a Nominal p-values for the linaclotide versus placebo comparisons for the 4 primary and 10 secondary efficacy parameters are presented unadjusted for multiplicity, as reported from the planned analyses of these parameters. After applying the prespecified serial gatekeeping MCP, all 14 comparisons were statistically significant. For categorical parameters, comparisons with placebo were based on the Cochran-Mantel-Haenszel test controlling for geographic region. For continuous parameters, comparisons with placebo were based on an ANCOVA model with treatment group and geographic region as factors and baseline value as a covariate. For change from baseline in 12-week percent of abdominal pain free days, p-value was obtained from ANCOVA models for the normal score of change from baseline with treatment group and geographic region as factors and normal score of baseline value as a covariate.

Table 23: Primary Efficacy Analysis: 9/12 Week Abdominal Pain and CSBM (APC) 3+1 Responders—ITT Population

	Placebo (N = 395)	Linaclotide (N = 405)	Statistics
Responder, n (%)	20 (5.1)	49 (12.1)	
Nonresponder, n (%)	375 (94.9)	356 (87.9)	
Difference in responder rate (linaclotide – placebo)	—	—	7.0
Odds ratio (95% CI)	—	—	2.60 (1.51, 4.47)
P-value	—	—	0.0004

A 9/12 week APC 3+1 responder was a patient who met the weekly APC 3+1 responder criteria for at least 9 of the 12 weeks of the double-blind treatment period.

Odds ratios, 95% CI and p-values were obtained from the Cochran-Mantel-Haenszel method controlling for geographic region.

The p-value met the criterion for statistical significance based on the multiple comparison procedure.

CI = confidence interval; CSBM = complete spontaneous bowel movement; ITT = intent-to-treat; N = population size; n = number of responders within a group.

For each week in the treatment period, a weekly APC 3+1 responder was a patient who had at least 3 CSBMs for the week and an increase of at least 1 CSBM from baseline for that week, and also had a decrease of at least 30% in the mean abdominal pain score for that week. The percentage of responders in the linaclotide treatment group

was over twice that in the placebo group (12.1% vs. 5.1%) with an odds ratio of 2.60 (p = 0.0004). See Table 23.

Table 24: Primary Efficacy Analysis: 9/12 Week CSBM 3+1 Responders—ITT Population

	Placebo (N = 395)	Linaclotide (N= 405)	Statistics
Responder, n (%)	25 (6.3)	79 (19.5)	
Nonresponder, n (%)	370 (93.7)	326 (80.5)	
Difference in responder rate (linaclotide – placebo)	—	—	13.2
Odds ratio (95% CI)	—	—	3.65 (2.26, 5.88)
P-value	—	—	<0.0001

A 9/12 week CSBM 3+1 responder was a patient who met the weekly CSBM 3+1 responder criteria for at least 9 of the 12 weeks of the double-blind treatment period.

Odds ratios, 95% CI and p-values were obtained from the Cochran-Mantel-Haenszel method controlling for geographic region.

The p-value met the criterion for statistical significance based on the multiple comparison procedure.

CI = confidence interval; CSBM = complete spontaneous bowel movement; ITT = intent-to-treat; N = population size; n = number of responders within a group.

The percentage of responders in the linaclotide treatment group for the 9/12 week CSBM 3+1 responders was over 3-times that in the placebo group (19.5% vs. 6.3%) with an odds ratio of 3.65 (p < 0.0001). See Table 24.

Table 25: Primary Efficacy Analysis: 9/12 Week Abdominal Pain Responders—ITT Population

	Placebo (N = 395)	Linaclotide (N= 405)	Statistics
Responder, n (%)	107 (27.1)	139 (34.3)	
Nonresponder, n (%)	288 (72.9)	266 (65.7)	
Difference in responder rate (linaclotide – placebo)	—	—	7.2
Odds ratio (95% CI)	—	—	1.41 (1.04, 1.91)
P-value	—	—	0.0262

9/12 week APC 3+1 responder was a patient who met the weekly APC 3+1 responder criteria for at least 9 of the 12 weeks of the double-blind treatment period.

Odds ratios, 95% CI and p-values were obtained from the Cochran-Mantel-Haenszel method controlling for geographic region.

The p-value met the criterion for statistical significance based on the multiple comparison procedure.

CI = confidence interval; CSBM = complete spontaneous bowel movement; ITT = intent-to-treat; N = population size; n = number of responders within a group.

The percentage of 9/12 week abdominal pain responders in the linaclotide treatment group was 34.3% compared with 27.1% in the placebo group (p = 0.0262). See Table 25.

Table 26: Sensitivity Analysis 9/12 Week Abdominal Pain and CSBM (APC) 3+1 Responders

Analysis	PLA	LIN	Diff (RFX-PLA)	P-value
(LOCF)	22/395 (5.6%)	74/405 (18.3%)	12.7%	<0.0001
Completed Case	17/255 (6.7%)	41/246 (16.7%)	10.0%	0.0005
Observed Case	20/389 (5.1%)	49/393 (12.5%)	7.4%	0.0003
Worst Case 1	17/395 (4.3%)	41/405 (10.1%)	5.8%	0.0015
Worst Case 2	157/395 (39.7%)	41/405 (10.1%)	-29.6%	<0.00001
Worst Case 3	48/395 (12.2%)	49/405 (12.1%)	-0.1%	0.9931
Multiple Imputation	5.3%	17.7%	12.5%	<0.0001

Compiled from Tables 14.4.1.1D-14.4.1.1.I and 14.4.1.1k

p-values were obtained from the CMH tests controlling for geographic region.

The complete case analysis includes only those patients who complete at least 4 IVRS calls for each of the first 12 weeks of treatment.

The observed case analysis includes only those patients who complete at least 4 IVRS calls for at least one of the first 12 weeks of treatment.

For worst case analysis 1, patients must complete at least 4 IVARS calls for each of the first 12 weeks of treatment.

For worst case analysis 2, patients who do not complete at least 4 IVRS call for each of the first 12 weeks of treatment are handled as follows: patients randomized to Linaclotide are non-responders, while patients who are randomized to placebo are considered responders.

For worst case analysis 3, for those weeks where patients do not complete at least 4 IVRS calls, patients randomized to Linaclotide are non-responders, while patients who are randomized to placebo are considered responders.

Medical Officer's Comments:

The sensitivity analysis shows similar results across difference types of analyses.

Table 27: Primary Efficacy Analysis: 6/12 Week APC +1 Responders—ITT Population

	Placebo (N = 395)	Linaclotide (N= 405)	Statistics
Responder, n (%)	83 (21.0)	136 (33.6)	
Nonresponder, n (%)	312 (79.0)	269 (66.54)	
Difference in responder rate (linaclotide – placebo)	—	—	12.6
Odds ratio (95% CI)	—	—	1.93 (1.40, 2.66)
P-value	—	—	< 0.0001

A 6/12 week APC +1 responder was a patient who met the weekly APC +1 responder criteria for at least 6 of the 12 weeks of the double-blind treatment period.

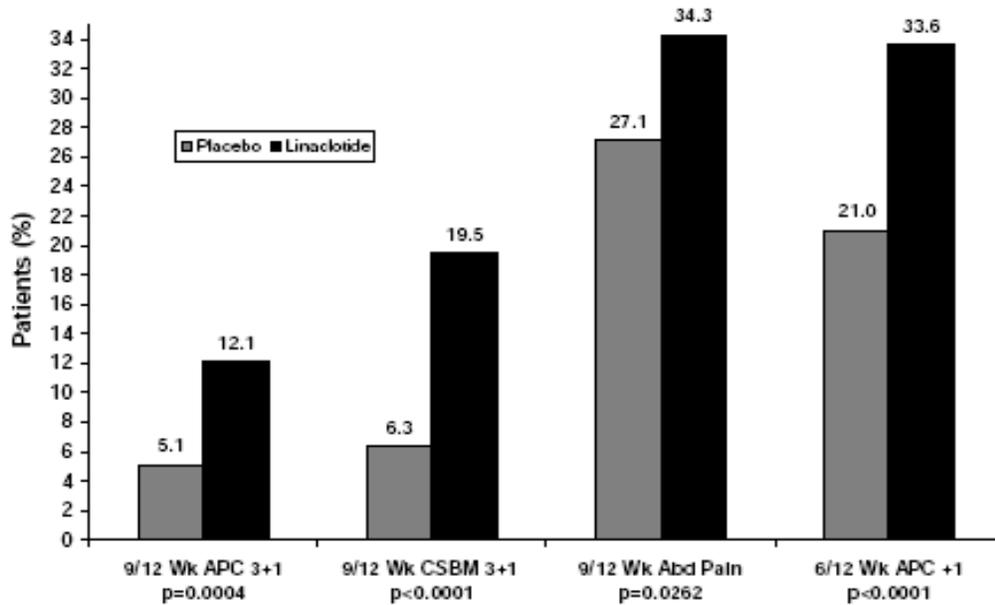
Odds ratios, 95% CI and p-values were obtained from the Cochran-Mantel-Haenszel method controlling for geographic region.

The p-value met the criterion for statistical significance based on the multiple comparison procedure.

CI = confidence interval; ITT = intent-to-treat; N = population size; n = number of responders within a group.

The percentage of 6/12 week APC +1 responders was 33.6% compared with 21.0% in the placebo group ($p < 0.0001$). See Table 27.

Figure 10: Primary Efficacy Parameter Responders



P-values were obtained from the Cochran-Mantel-Haenszel tests controlling for geographic region, comparing linacotide versus placebo. All p-values met the criterion for statistical significance based on the multiple comparison procedure.

Exploratory analysis of Primary endpoints

Exploratory analyses of the co-primary endpoints by week and month was requested from the Applicant and shows statistically significant results in favor of linaclotide for all weeks and months of the trial. See Table 28 and Table 29.

Table 28: Weekly Abdominal Pain and CSBM (APC) 3 + 1 Responder Rate by Treatment Group

Study LIN-MD-31				
	PLA	LIN	Diff (LIN-PLA)	Chi-square p-value
Week 1	24/395 (6.1%)	70/405 (17.3%)	11.2%	<0.0001
Week 2	40/395 (10.1%)	82/405 (20.2%)	10.1%	<0.0001
Week 3	32/395 (8.1%)	102/405 (25.2%)	17.1%	<0.0001
Week 4	49/395 (12.4%)	114/405 (28.1%)	15.7%	<0.0001
Week 5	46/395 (11.6%)	101/405 (24.9%)	13.3%	<0.0001
Week 6	53/395 (13.4%)	110/405 (27.2%)	13.8%	<0.0001
Week 7	53/395 (13.4%)	96/405 (23.7%)	10.3%	<0.0001
Week 8	53/395 (13.4%)	98/405 (24.2%)	10.8%	<0.0001
Week 9	55/395 (13.9%)	92/405 (22.7%)	8.8%	0.0013
Week 10	46/395 (11.6%)	86/405 (21.2%)	9.6%	0.0002
Week 11	55/395 (13.9%)	88/405 (21.7%)	7.8%	0.0038
Week 12	43/395 (10.9%)	90/405 (22.2%)	11.3%	<0.0001

Compiled by Milton Fan, PhD. from Table 14.4.1.1C

P-values were obtained by the CMH tests controlling for geographic region.

Table 29: Monthly Abdominal Pain and CSBM (APC) 3 + 1 Responder Rate by Treatment Group

Study LIN-MD-31				
	PLA	LIN	Diff (LIN-PLA)	Chi-square p-value
Month 1	43/395 (10.9%)	106/405 (26.2%)	15.3%	<0.0001
Month 2	58/395 (14.7%)	112/405 (27.7%)	13.0%	<0.0001
Month 3	57/395 (14.4%)	102/405 (25.2%)	10.8%	0.0001

Compiled by Milton Fan, PhD. from Table 14.4.1.1C

P-values were obtained by the CMH tests controlling for geographic region.

5.3.2.8 Analysis of Secondary Endpoints(s)

Medical Officer's Comments:

While the majority of the secondary endpoints reach statistically significant p-values, many of the endpoints (e.g., straining, bloating and abdominal discomfort) are poorly defined, not validated and may not be clinically meaningful.

Over the 12-week treatment period, the patients treated with linaclotide showed improvement relative to placebo in all of the secondary efficacy parameters. Statistical

significance after controlling for multiplicity was met for all tests of the secondary efficacy parameters.

Table 30: Overview of Primary and Secondary Efficacy Parameters for the 12-Week Treatment Period—ITT Population

Secondary Efficacy Parameters					
Parameter	Baseline Mean (SD)	Placebo (N = 395)	Linaclootide (N = 405)	Statistics	
		LSMC (SE)	LSMC (SE)	LSMD (95% CI)	P-value ^a (Significant by MCP)
Change from baseline in CSBM frequency rate	0.22 (0.48)	0.705 (0.128)	2.272 (0.127)	1.568 (1.241, 1.895)	< 0.0001 (yes)
Change from baseline in SBM frequency rate	1.92 (1.39)	1.130 (0.177)	3.898 (0.176)	2.769 (2.315, 3.223)	< 0.0001 (yes)
Change from baseline in stool consistency	2.34 (1.02)	0.662 (0.061)	2.071 (0.060)	1.409 (1.253, 1.565)	< 0.0001 (yes)
Change from baseline in severity of straining	3.50 (0.79)	-0.651 (0.042)	-1.306 (0.042)	-0.655 (-0.763, -0.546)	< 0.0001 (yes)
Change from baseline in abdominal pain	5.64 (1.68)	-1.129 (0.094)	-1.869 (0.093)	-0.740 (-0.981, -0.499)	< 0.0001 (yes)
Change from baseline in abdominal discomfort	6.11 (1.64)	-1.211 (0.097)	-1.953 (0.096)	-0.742 (-0.990, -0.494)	< 0.0001 (yes)
Change from baseline in bloating	6.61 (1.83)	-1.100 (0.100)	-1.944 (0.099)	-0.844 (-1.101, -0.587)	< 0.0001 (yes)
Change from baseline in 12 week percent of abdominal pain-free days	1.88 (6.25)	5.31b (0.79)	9.81b (1.08)	N/A	0.0014c (yes)

5.3.2.9 Other Endpoints

Medical Officer's Comments:

These other endpoints are exploratory, poorly defined and not validated; as such the clinical meaningfulness is questionable.

Table 31: Additional Efficacy Analyses: Efficacy Assessment Responders—ITT Population

Efficacy Parameter	Placebo (N = 395)		Linaclotide (N = 405)		P-value
	N ₁	n (%)	N ₁	n (%)	
9/12 week abdominal discomfort responder	395	95 (24.1)	405	130 (32.1)	0.0107
9/12 week APC + 1 responder	395	42 (10.6)	405	72 (17.8)	0.0037
9/12 week bloating responder	395	71 (18.0)	405	111 (27.4)	0.0013
9/12 week constipation severity responder	395	100 (25.3)	405	189 (46.7)	< 0.0001
9/12 week CSBM + 1 responder	395	68 (17.2)	405	131 (32.3)	< 0.0001
9/12 week CSBM 3 responder	395	26 (6.6)	405	80 (19.8)	< 0.0001
9/12 week IBS symptom severity responder	395	96 (24.3)	405	166 (41.0)	< 0.0001
9/12 week SBM + 2 responder	395	58 (14.7)	405	165 (40.7)	< 0.0001
9/12 week severity of straining responder	348	54 (15.5)	360	143 (39.7)	< 0.0001
9/12 week stool consistency responder	348	12 (3.4)	360	96 (26.7)	< 0.0001
6/12 week abdominal discomfort responder	395	146 (37.0)	405	195 (48.1)	0.0013
6/12 week APC 3 + 1 responder	395	39 (9.9)	405	93 (23.0)	< 0.0001
6/12 week bloating responder	395	118 (29.9)	405	176 (43.5)	0.0001
6/12 week constipation severity responder	395	168 (42.5)	405	241 (59.5)	< 0.0001
6/12 week CSBM 3 + 1 responder	395	50 (12.7)	405	129 (31.9)	< 0.0001
6/12 week CSBM 3 responder	395	51 (12.9)	405	130 (32.1)	< 0.0001
6/12 week IBS symptom severity responder	395	148 (37.5)	405	228 (56.3)	< 0.0001
6/12 week SBM + 2 responder	395	116 (29.4)	405	233 (57.5)	< 0.0001
6/12 week severity of straining responder	348	94 (27.0)	360	205 (56.9)	< 0.0001
6/12 week stool consistency responder	348	26 (7.5)	360	151 (41.9)	< 0.0001

CSBM = complete spontaneous bowel movement; N = population size; N₁ = Number of evaluable patients; n = number of responders within a group; SBM = spontaneous bowel movement.

5.3.2.10 Subpopulations

Table 32: Subgroup Analyses of Proportion of 9/12 Week Abdominal Pain and CSBM (APC) 3+1 Responders

Subgroup	Placebo	Linaclotide	(LIN-PLA)	95% CI
Gender				
Male	0/38 (0.0%)	4/38 (10.5%)	10.5%	(10.2%, 10.8%)
Female	20/357 (5.6%)	45/367 (12.2%)	6.7%	(6.5%, 6.8%)
Age				
<65	16/369 (4.3%)	47/386 (12.2%)	7.8%	(7.7%, 8.0%)
≥65	4/26 (15.4%)	2/19 (10.5%)	-4.9%	(-5.5%, -4.2%)
Race				
White	17/301 (5.6%)	41/314 (13.1%)	7.4%	(7.3%, 7.6%)
Black	2/75 (2.7%)	7/78 (9.0%)	6.3%	(6.1%, 6.5%)
Other	1/19 (5.3%)	1/13 (7.7%)	2.4%	(1.9%, 3.0%)
BMI at baseline				
< 30 kg/m ²	18/275 (6.5%)	25/271 (9.2%)	2.7%	(2.5%, 2.8%)
≥ 30 kg/m ²	2/120 (1.7%)	24/134 (17.9%)	16.2%	(16.0%, 16.5%)
Abdominal Pain at Baseline				
< 5	9/156 (5.8%)	16/152 (10.5%)	4.8%	(4.6%, 5.0%)
≥ 5 < 8	8/198 (4.0%)	31/214 (14.5%)	10.5%	(10.3%, 10.6%)
≥ 8	3/41 (7.3%)	2/39 (5.1%)	-2.2%	(-2.5%, -1.9%)

Compiled by Milton Fan, PhD from Table 14.4.1.1J

Medical Officer's Comments:

As seen from Table 32 above, the subgroup analysis differs from the results for Trial MCP-301-102, in that those with a BMI > 30 kg/m² were more likely to be responders, however since the number of patients is low, the results are not statistically significant and may not be clinically meaningful.

5.3.2.11 Analysis of Clinical Information Relevant to Dosing Recommendations

See discussion in Section

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations on page 108.

5.3.2.12 Discussion of Persistence of Efficacy and/or Tolerance Effects – Evaluation of Randomized Withdrawal Period

Disposition

Of the 335 patients treated with placebo who completed the 12-week double-blind treatment period, 333 received at least 1 dose of linaclotide 266 µg during the randomized withdrawal (RW) period and were included in the RW Population. Of the 312 patients treated with linaclotide who completed the double-blind treatment period, 154 were rerandomized to placebo and 158 were rerandomized to continue linaclotide during the RW period and were included in the RW Population. About 97% of patients completed the 4 weeks of double-blind treatment during the RW period.

Table 33: Number (%) of Patients Discontinued From the Study during the Randomized Withdrawal Period

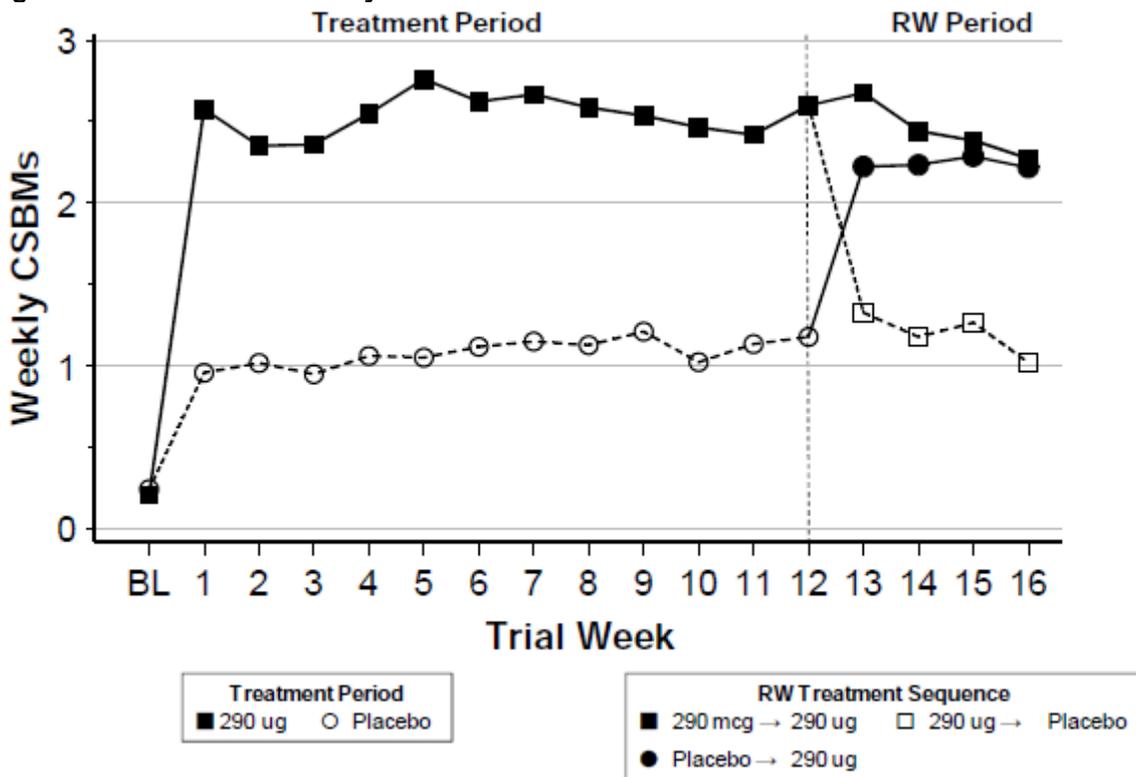
	Placebo / Lin (N = 335^a)	Lin / Placebo (N = 154)	Lin / Lin (N = 158)
	n (%)	n (%)	n (%)
RW Population	333 (99.4)	154 (100)	158 (100)
Completed RW Period	325 (97.0)	151 (98.1)	154 (97.5)
Discontinued from RW period	10 (3.0)	3 (1.9)	4 (2.5)
Reason for discontinuation			
Adverse event	2 (0.6)	1 (0.6)	0
Protocol violation	1 (0.3)	1 (0.6)	2 (1.3)
Withdrawal of consent	2 (0.6)	0	0
Lost to follow-up	3 (0.9)	0	2 (1.3)
Insufficient therapeutic response	0	1 (0.6)	0
Other	2 (0.6)	0	0

^a Includes 2 patients who were assigned linaclotide but did not receive any treatment during the RW period.
 RW = randomized withdrawal

Overall, treatment compliance was greater than 90% in each treatment sequence. Overall, and at each week of the 4-week RW period, over 60% of patients in each treatment sequence had ≥ 80% complete calls.

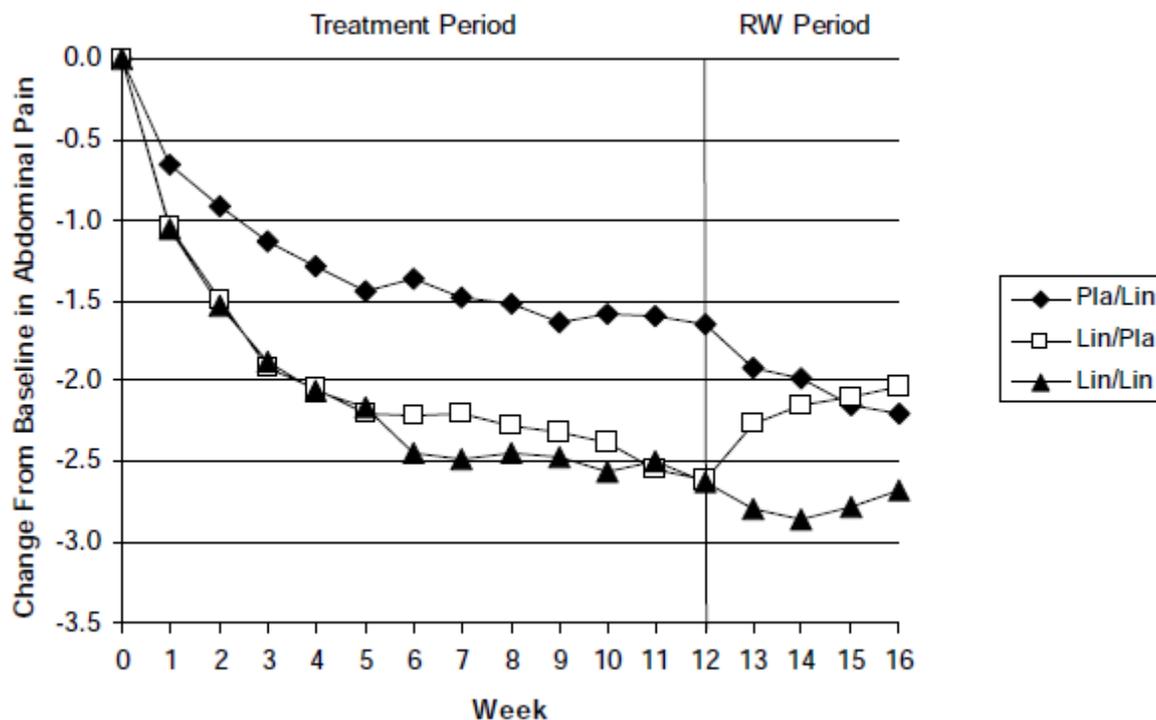
Figure 11 presents the change from baseline in weekly CSBM Rate over the entire 16 weeks of LIN-MD-31, which includes both the 12-week Treatment Period and the 4-week RW Period. The patients remaining on their linaclotide dose showed sustained improvements in CSBM Frequency Rate during the RW Period that were almost identical to those experienced by linaclotide patients during the Treatment Period. Patients re-randomized from linaclotide to placebo in the RW Period showed a rapid decline in their improvements to a level similar to that observed in placebo patients during the Treatment Period. These patients were aware they were re-randomized and may or may not be getting the active ingredient.

Figure 11: Mean CSBM Rate by Week over the Entire 16-week LIN-MD-31 Trial



For Abdominal Pain, the patients remaining on their linaclotide dose showed sustained improvements in Abdominal Pain during the RW Period that were almost identical to those experienced by linaclotide patients during the Treatment Period. Patients re-randomized from linaclotide to placebo in the RW Period showed a decline in their improvements to a level similar to that observed in placebo patients during the Treatment Period.

Figure 12: Change From Baseline in Mean Abdominal Pain during Each Week of Study (OC)—RW Population



Lin = linaclotide; OC = observed cases; Pla = placebo; RW = randomized withdrawal

These results indicate that persistence of treatment effect is dependent upon continued linaclotide dosing. Furthermore, there was no evidence of development of tolerance, nor was there evidence of rebound worsening relative to baseline once the drug was discontinued.

The Applicant summarized the data for the RW period as follows: At the end-of-treatment phase (ETP) the patients in the RW Population who were treated with placebo had a less robust response to treatment compared with the patients treated with linaclotide. This was true for both bowel habits and abdominal symptoms. However, after the placebo patients were treated with linaclotide for 4 weeks during the RW period, there was an improvement in all of these parameters, approaching the improvement attained by the linaclotide patients at the end of the 12-

week treatment period. In contrast, patients who were treated with linaclotide during the treatment period, and then rerandomized to placebo in the RW period had a decrease in the improvements attained over the course of linaclotide treatment. There was no evidence of a rebound effect after linaclotide withdrawal. The patients who were treated with linaclotide during the treatment period and then rerandomized to linaclotide during the 4 weeks of the RW period maintained the level of response to linaclotide treatment for all of the efficacy parameters.

Table 34: Overview of Efficacy Parameters during the Combined Treatment and Randomized Withdrawal Periods—RW Population

Parameter	Placebo - Lin (N =333)	Lin- Placebo (N = 154)	Lin-Lin (N = 158)
Mean ± SD (n)	Mean ± SD (n)	Mean ± SD (n)	
Change From Baseline in CSBM Frequency Rate			
At End of Treatment Period	0.940 ± 1.766 (333)	2.405 ± 3.265 (154)	2.446 ± 3.412 (158)
At End of Study	1.990 ± 2.767 (333)	0.988 ± 1.751 (154)	2.296 ± 2.917 (158)
Change From Baseline in SBM Frequency Rate			
At End of Treatment Period	1.308 ± 2.617 (333)	4.000 ± 4.251 (154)	4.012 ± 4.286 (158)
At End of Study	3.107 ± 3.905 (333)	1.624 ± 2.597 (154)	3.788 ± 3.760 (158)
Change From Baseline in Stool Consistency			
At End of Treatment Period	0.717 ± 1.367 (255)	2.061 ± 1.643 (123)	2.231 ± 1.582 (126)
At End of Study	1.869 ± 1.451 (284)	0.956 ± 1.342 (128)	2.195 ± 1.518 (132)
Change From Baseline in Severity of Straining			
At End of Treatment Period	-0.793 ± 1.005 (255)	-1.453 ± 0.917 (123)	-1.497 ± 1.075 (126)
At End of Study	-1.228 ± 1.017 (284)	-1.019 ± 0.934 (128)	-1.471 ± 1.037 (132)
Change From Baseline in Abdominal Pain			
At End of Treatment Period	-1.646 ± 2.117 (330)	-2.610 ± 2.110 (150)	-2.621 ± 2.322 (157)
At End of Study	-2.059 ± 2.102 (332)	-2.143 ± 2.092 (150)	-2.787 ± 2.286 (158)
Change From Baseline in Abdominal Discomfort			
At End of Treatment Period	-1.720 ± 2.182 (330)	-2.611 ± 2.237 (150)	-2.803 ± 2.467 (157)
At End of Study	-2.113 ± 2.120 (332)	-2.148 ± 2.157 (150)	-2.919 ± 2.458 (158)
Change From Baseline in Bloating			
At End of Treatment Period	-1.595 ± 2.213 (330)	-2.490 ± 2.408 (150)	-2.917 ± 2.681 (157)
At End of Study	-2.068 ± 2.282 (332)	-2.078 ± 2.198 (150)	-3.071 ± 2.669 (158)
Change From Baseline in Percent of Abdominal Pain-Free Days			
At End of Treatment Period	7.748 ± 23.299 (330)	12.157 ± 27.200 (150)	15.558 ± 34.007 (157)
At End of Study	9.715 ± 24.716 (332)	9.153 ± 22.558 (150)	16.644 ± 33.785 (158)

End of Treatment Period refers to the end of Week 12 of the Treatment Period for patients included in the RW Population; End of Study refers to the end of the overall 4-Week RW Period for patients included in the RW Population.

CSBM = complete spontaneous bowel movement; N = population size; n = number of patients with available analysis at both baseline and specified time point; SBM = spontaneous bowel movement.

Lin = linaclotide; OC = observed cases; Pla = placebo; RW = randomized withdrawal.

As shown in Table 35, when patients were switched from placebo to linaclotide there was a decrease in the use of rescue medications. At baseline, the median percentage of days with rescue medication use was 7.69 in both treatment groups. In contrast, patients who were switched from linaclotide to placebo during the RW period had an increase in days of rescue medication use, while patients who remained on linaclotide had no meaningful change in the use of rescue medications.

Table 35: Change From Baseline in Percentage of Days of Rescue Medication Use during the Combined Treatment and Randomized Withdrawal Periods—RW Population

Parameter	Placebo / Lin (N = 333)	Lin / Placebo (N = 154)	Lin / Lin (N = 158)
	Mean ± SD	Mean ± SD	Mean ± SD
At End of Treatment Period	-2.03 ± 17.37	-6.56 ± 16.25	-8.02 ± 15.85
At End of Study	-5.73 ± 18.81	-4.47 ± 16.87	-8.77 ± 15.99

IBS-SSS

Medical Officer's Comments:

The applicant evaluated the IBS-SSS (symptom severity score) however, the IBS-SSS is not a validated tool for measuring symptom severity in these patients and therefore this data will not be presented.

5.3.2.13 Additional Efficacy Issues/Analyses

Duplicate Patients

The results of these sensitivity analyses indicate that there was no meaningful impact of the duplicate patients on the primary efficacy results for LIN-MD-31.

Table 36: Results of Duplicate Patient Sensitivity Analysis for the Primary Efficacy Parameters for LIN-MD-31

Parameter		Primary Analysi s N = 800	Excluding All Duplicate- Patient Data N = 789	Including All Duplicate- Patient Data N = 802
9/12 Week APC 3 + 1 Responder	Placebo n/N (%)	20/395 (5.1)	20/390 (5.1)	20/395 (5.1)
	Linaclotide n/N (%)	49/405 (12.1)	48/399 (12.0)	50/407 (12.3)
	p-value	0.0004	0.0005	0.0003
9/12 Week CSBM 3 + 1 Responder	Placebo n/N (%)	25/395 (6.3)	25/390 (6.4)	25/395 (6.3)
	Linaclotide n/N (%)	79/405 (19.5)	78/399 (19.5)	80/407 (19.7)
	p-value	< 0.0001	< 0.0001	< 0.0001
9/12 Week Abdominal Pain Responder	Placebo n/N (%)	107/395 (27.1)	105/390 (26.9)	107/395 (27.1)
	Linaclotide n/N (%)	139/405 (34.3)	137/399 (34.3)	140/407 (34.4)
	p-value	0.0262	0.0234	0.0240
6/12 Week APC +1 Responder	Placebo n/N (%)	83/395 (21.0)	83/390 (21.3)	83/395 (21.0)
	Linaclotide n/N (%)	136/405 (33.6)	133/399 (33.3)	138/407 (33.9)
	p-value	< 0.0001	0.0001	< 0.0001

p-value based on the CMH test controlling for trial and geographic region.

6 Review of Efficacy

Efficacy Summary

For the reviewed indication of Irritable Bowel Syndrome with Constipation (IBS-C), linaclotide provided substantive evidence of efficacy over placebo in two large, randomized, placebo-controlled, multi-center, phase 3 trials (MCP-103-302 and LIN-MD-31) and the combined analysis.

The applicant provided data to support efficacy for four primary endpoints in both trials, as well as multiple secondary endpoints:

- Two of the four primary endpoints were co-primary endpoints of improvement in both abdominal pain and stool frequency.
 - The first primary endpoint was improvement of at least 30% in abdominal pain and, increase in complete spontaneous bowel movement (CSBM) to at least 3 per week plus 1 more than baseline in 9 of 12 weeks of the primary efficacy period (9/12 week APC 3+1 Responder).
 - The second co-primary endpoint was 6 of 12 weeks of improvement in abdominal pain (AP) and CSBM of plus 1 over baseline (6/12 week APC +1 Responder).
- The other two primary endpoints evaluated 9/12 weeks 30% improvement in abdominal pain and 9/12 week CSBM 3+1.

The applicant elected to test only one dose (290µg) in the phase 3 IBS-C trials, even though a clear dose-response for efficacy endpoints was not noted in this Phase 2b trial for linaclotide in IBS-C. The applicant did test two doses (145µg and 290µg) in the phase 3 Chronic Constipation (CIC) trials. Efficacy was comparable in the two doses in the CIC trials, (b) (4)

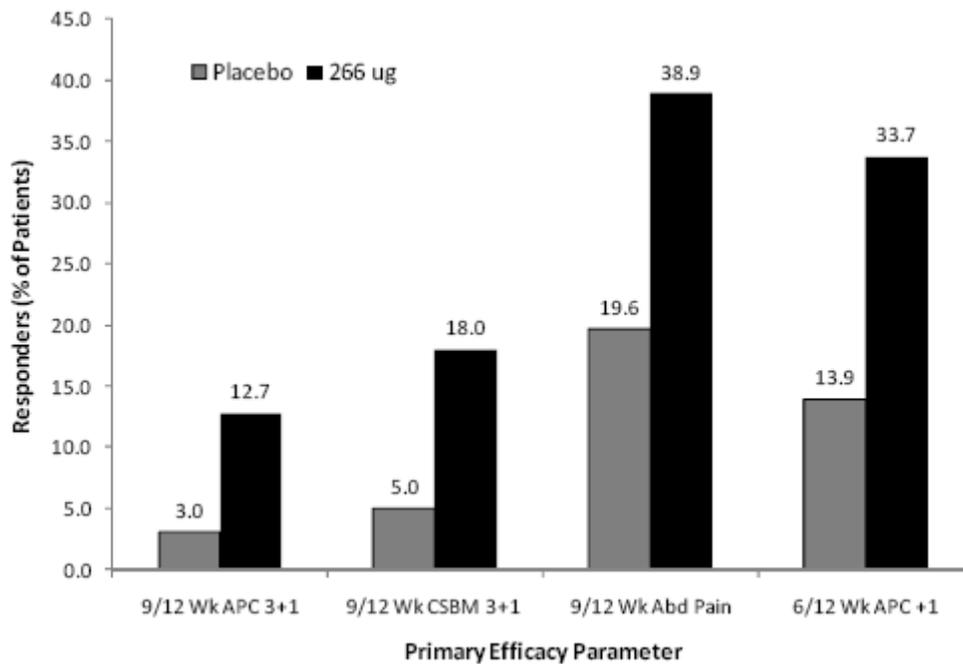
Evaluation of the efficacy of the 145µg dose in IBS-C patients would have been optimal. See discussion in Section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations – Review of Dose Ranging Trials on page 108.

MCP-103-302

MCP-103-302 was a 26 week trial but the primary efficacy period was for the first 12 weeks. This trial enrolled 805 male and female patients who met modified Rome II criteria for IBS-C received once-daily linaclotide 290 ug or placebo. Demographics and baseline characteristics were balanced across the treatment groups. Study MCP-103-302 results show that linaclotide was statistically significantly better than placebo in terms of the primary efficacy endpoint, 9/12 week APC 3+1 Responder. The treatment difference was 9.7%. Linaclotide was also statistically better than placebo in terms of the other three primary efficacy endpoints. The treatment differences ranged from 13% to 20% (See

Figure 15). Superiority was also shown for some of the secondary efficacy 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, CSBM frequency rate, and change from baseline in 12-week percent of abdominal pain-free days. Secondary and exploratory analysis provided evidence of persistence of effect throughout the 26 weeks of the trial.

Figure 13: Primary Efficacy Results from MCP-103-302



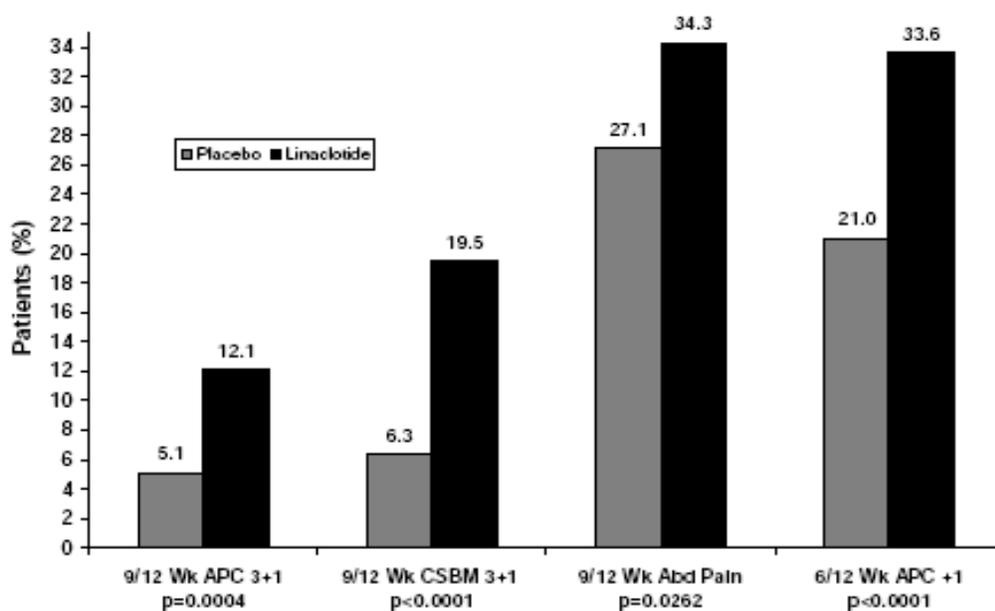
LIN-MD-31

LIN-MD-31 employed a 4 week randomized withdrawal after 12 weeks of treatment period. In this trial, 802 male and female patients who met modified Rome II criteria for IBS-C received once-daily linaclotide 290µg or placebo for 12 weeks. Demographics and baseline characteristics were balanced across the treatment groups. Study LIN-MD-31 showed statistically significant results for primary efficacy endpoint of 9/12 week APC 3+1 Responder. However, the treatment difference was not as robust at 7.0%. The treatment difference for the 6/12 week APC +1 was 12.6%. All four primary endpoints showed statistically significant efficacy at 12 weeks (See Figure 16). Additionally, the 290µg linaclotide dose group demonstrated improvement compared to the placebo

group for each of the secondary efficacy parameters (all p-values $p \leq 0.05$ and statistically significant after controlling for multiplicity).

The results of the Randomized Withdrawal Period indicate that persistence of treatment effect is dependent upon continued linaclotide dosing. Furthermore, there was no evidence of development of tolerance, nor was there evidence of rebound worsening relative to baseline once the drug was discontinued.

Figure 14: Primary Efficacy Results from LIN-MD-31



As per request, the sponsor provided exploratory analysis of the number of subjects with $\geq 30\%$ improvement of abdominal pain and CSBM of 3 +1 by week and by month. Greater proportions of patients showed efficacy at almost every week and every month during both the 26-week study (MCP-103-302) (See Table 14 and Table 15 on page 58) and the 12 week trial (LIN-MD-31) in the linaclotide group as compared with patients in the placebo group. See (Table 28 and Table 29 on page 82).

Sensitivity analyses were supportive of the primary analysis in both trials. Subpopulation analyses did not show any significant differences in efficacy among subpopulations.

In conclusion, both studies (MCP-103-302 and LIN-MD-31) showed that linaclotide was superior to the placebo for protocol-specified primary endpoints of improvement in abdominal pain and stool consistency. Exploratory analyses of trial data indicate that the improvement in stool consistency occurred more rapidly than improvement in

abdominal pain There is evidence of efficacy in men, though they comprise only approximately 10% of the trial population, they show statistically significant efficacy in two of the four primary endpoints and trends toward efficacy in the other two primary endpoints (See discussion in Section 6.1.7 Subpopulations on page 104). There was evidence of persistence of efficacy during the 26 week trial and no evidence of rebound during the randomized withdrawal period. Ideally, the 145µg dose would have been studied in the IBS-C population, as it was in the CIC population, for the reasons stated above.

6.1 Indication

Irritable Bowel Disease with constipation
See discussion in Section 5.3.1.1 Indication

6.1.1 Methods

See discussion in Section 5.3.1.2 Methods on page 40, and 5.3.2.2 Methods on page 69

6.1.2 Demographics

The majority of patients in the IBS-C Phase 3 Pooled Population were Caucasian (77.4%) and female (90.1%). Mean age for all patients was 43.9 years. A total of 85 patients (5.3%) were ≥ 65 years of age. There were 159 male patients (9.9%), 301 (18.8%) black patients, and 193 (12.0%) Hispanic/Latino patients in the pooled population. See Table 37, next page.

Table 37: Demographic and Baseline Characteristics (IBS-C Phase 3 Pooled ITT Population)

Demographic Characteristic	Placebo (N = 797)	290 ug (N = 805)	Total (N = 1602)
Age, years			
Mean (SD)	43.8 (13.1)	44.0 (12.9)	43.9 (13.0)
Median (Min, Max)	44.0 (18, 87)	44.0 (19, 82)	44.0 (18, 87)
Age, n (%)			
< 65 years	754 (94.6)	763 (94.8)	1517 (94.7)
65 to < 75	35 (4.4)	30 (3.7)	65 (4.1)
≥ 75 years	8 (1.0)	12 (1.5)	20 (1.2)
Sex, n (%)			
Female	708 (88.8)	735 (91.3)	1443 (90.1)
Male	89 (11.2)	70 (8.7)	159 (9.9)
Race, n (%)			
Black	153 (19.2)	148 (18.4)	301 (18.8)
Caucasian	611 (76.7)	629 (78.1)	1240 (77.4)
Other	33 (4.1)	28 (3.5)	61 (3.8)
Ethnicity, n (%)			
Hispanic/Latino	94 (11.8)	99 (12.3)	193 (12.0)
Not Hispanic/Latino	703 (88.2)	706 (87.7)	1409 (88.0)
Height, cm			
Mean (SD)	165.1 (8.1)	164.9 (8.1)	165.0 (8.1)
Median (Min, Max)	165.1 (139.7, 195.6)	165.0 (134.6, 194.0)	165.1 (134.6, 195.6)
Weight, kg			
Mean (SD)	75.5 (18.4)	76.4 (18.5)	75.9 (18.4)
Median (Min, Max)	72.6 (43.0, 182.4)	73.5 (43.6, 173.6)	73.0 (43.0, 182.4)

BMI, kg/m ²			
Mean (SD)	27.7 (6.2)	28.0 (6.2)	27.8 (6.2)
Median (Min, Max)	26.4 (15.2, 64.9)	27.1 (17.7, 58.2)	26.8 (15.2, 64.9)

The IBS-C Phase 3 Pulled ITT Population consists of all patients in the ITT Populations for the two Phase 3 double-blind, placebo-controlled, IBS-C trials.

No p-values ≤ 0.05 comparing each demographic characteristic between linaclotide and placebo.

p-values for continuous variables (e.g., age, weight, height, BMI) are from an ANOVA with trial, treatment group and geographic region as factors; p-values for categorical variables (e.g., sex, ethnicity, and race) are from a CMH test controlling for trial and geographic region.

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 meters squared.

The baseline disease characteristics underlying the secondary efficacy parameters for bowel symptoms (CSBMs/week, Stool Consistency, Severity of Straining,) were similar across the Phase 3 placebo-controlled studies as well as among the treatment groups within each of the studies (MCP-103-302, and LIN-MD-31). Across the two Phase 3 trials the baseline abdominal symptoms severities were similar. The IBS-C patient population studied in the linaclotide clinical program appears to be representative of the general IBS-C patient population

6.1.3 Subject Disposition

A total of 1606 patients were randomized in the two Phase 3 IBS-C efficacy trials. At least 74% of the enrolled patients completed each of the studies. More patients on placebo than linaclotide prematurely discontinued from the Phase 3 trial MCP-103-302 for insufficient therapeutic response.

A total of 364 (22.7%) of 1606 patients prematurely discontinued; more patients on placebo discontinued due to insufficient therapeutic response when compared with linaclotide.

Table 38: Patient Disposition (IBS-C Phase 3 Pooled Randomized Population)

	Placebo (N = 799) n (%)	290 ug (N = 807) n (%)	Total (N = 1606) n (%)
Completed Treatment Period ^a	637 (79.7)	605 (75.0)	1242 (77.3)
Prematurely Discontinued	162 (20.3)	202 (25.0) ^b	364 (22.7)
Reason for Premature Discontinuation			
Adverse Event	21 (2.6)	73 (9.0) ^c	94 (5.9)
Protocol Violation	20 (2.5)	18 (2.2)	38 (2.4)
Withdrawal of Consent	52 (6.5)	49 (6.1)	101 (6.3)
Lost to Follow-up	23 (2.9)	35 (4.3)	58 (3.6)
Insufficient Therapeutic Response	37 (4.6)	20 (2.5) ^b	57 (3.5)
Study Terminated by Sponsor	0	0	0
Other Reasons	9 (1.1)	7 (0.9)	16 (1.0)

N = Number of patients in the Randomized Population (all randomized patients from the two Phase 3 double-blind, placebo-controlled, IBS-C studies).

n = Number of patients within a specific category.

Treatment period for MCP-103-302 and LIN-MD-31 is 26 weeks and 12 weeks, respectively.

P-values are from a comparison with placebo group using the Fisher exact test.

a. Patients who stayed on-study through visit 7 (Week 12) and then were re-randomized for entry into the RW Period are counted as completing treatment.

b. $p \leq 0.05$

c. $p < 0.0001$

6.1.4 Analysis of Primary Endpoint(s)

Consistent with the results of the two Phase 3 IBS-C trials, which each demonstrated statistically significant improvement for the primary and secondary efficacy parameters, there was a separation in the IBS-C Phase 3 Pooled ITT Population between linaclotide 290 ug and placebo for each of the 4 primary efficacy parameters ($p < 0.0001$).

Table 39: Pooled Phase 3 IBS-C Primary Efficacy Results

<i>Phase 3 Primary Efficacy Parameters</i>	<i>Placebo (N=797)</i>	<i>Linaclotide 290 ug (N=805)</i>
9/12 Week APC 3+1 Responder		
Responder, n (%)	32 (4.0)	100 (12.4) ^a
Odds Ratio (95% CI)		3.4 (2.2, 5.1)
Difference in Responder Rate (Linaclotide - Placebo) (%)		8.4
9/12 Week CSBM 3+1 Responder		
Responder, n (%)	45 (5.6)	151 (18.8) ^a
Odds Ratio (95% CI)		3.9 (2.7, 5.5)
Difference in Responder Rate (Linaclotide - Placebo) (%)		13.1
9/12 Week Abdominal Pain Responder		
Responder, n (%)	186 (23.3)	295 (36.6) ^a
Odds Ratio (95% CI)		1.9 (1.5, 2.4)
Difference in Responder Rate (Linaclotide - Placebo) (%)		13.3
6/12 Week APC +1 Responder		
Responder, n (%)	139 (17.4)	271 (33.7) ^a
Odds Ratio (95% CI)		2.4 (1.9, 3.1)
Difference in Responder Rate (Linaclotide - Placebo) (%)		16.2

CI = confidence interval p-value: comparison of linaclotide versus placebo obtained from CMH test controlling for trial and geographic region

a - p < 0.0001 Source: IBS-C Phase 3 Pooled ITT After-text Applicant Tables 3.1.1, 3.2.1, 3.3.1, 3.4.1

6.1.5 Analysis of Secondary Endpoints(s)

For each of the Phase 3 trials, the 12-week LS mean differences between linaclotide 290 ug and placebo for all of the change-from-baseline secondary efficacy parameters were statistically significant.

Table 40: Overview of Secondary Efficacy Parameter Results (IBS-C Phase 3 Pooled ITT Population)

12-week Parameter	Mean Baseline	Mean Change from Baseline (SE)		
		Placebo (N = 797)	Linaclotide 290 ug ^a (N = 805)	LSMD (95% CI)
CSBMs/Week	0.2	0.7 (0.1)	2.20(0.1) ^a	1.6 (1.3,1.8)
SBMs/Week	1.8	1.2(0.1)	3.90(0.1)	2.7 (2.4, 3.1)
Stool Consistency (BSFS Score)	2.3	0.6 (0.0)	2.0 (0.0)	2.7 (2.4, 3.1)
Straining (5-point Ordinal Scale)	3.5	-0.6 (0.0)	-1.3 (0.0)	-0.6 (-0.7, -0.5)
Abdominal Pain at its Worst (11-point NRS)	5.6	-1.1 (0.1)	-1.8 (0.1)	-0.8 (-0.9,-0.6)
Abdominal Discomfort (11-point NRS)	6.1	-1.1 (0.1)	-1.9 (0.1)	-0.8 (-1.0, -0.7)
Bloating (11-point NRS)	6.6	-1.0 (0.1)	-1.9 (0.1)	-0.9 (-1.0, -0.7)
Percent of Abdominal Pain-free Days	2.0	5.1 (16.2)	10.2 (22.6)	5.1 (3.2, 7.0)

For Percent of Abdominal Pain-free Days, the mean change from baseline (SD) and the mean difference (CIs) are presented.

Baseline is the mean value for the combined ITT Population.

SE = standard error of LS mean; CI = Confidence interval; LSMD = Least squares mean difference

p-values for change-from-baseline secondary efficacy parameters based on a comparison of linaclotide versus placebo in an ANCOVA model with treatment group, trial, and geographic region as factors and baseline value as covariate.

p-values for responder secondary efficacy parameters based on the CMH test controlling for trial and geographic region.

The mean change from baseline is a least-squares mean change based on an ANCOVA model.

a. p < 0.0001

6.1.6 Other Endpoints

Medical Officer's Comments:

These other endpoints are exploratory, poorly defined and not validated; as such the clinical meaningfulness is questionable. The formulation of the clinical meaningfulness questions do not follow the guidelines mentioned in the IBS Guidance for Industry, as the answer requires recall over several months.

Clinical Meaningfulness

Patients were asked to rate their relief/improvement for each specific symptom (such as abdominal pain) as well as to rate their overall degree of relief; in both cases, patients

were asked to compare their relief during the trial to how they felt before starting the trial as a point of reference. The responses to these patient rating of change questions provides a method for mapping a particular efficacy result to a level of improvement as reported by the patient. An example of a symptom-specific “Patient Rating of Change” (PRCQ) question is:

For each of the 4 primary parameters, patients were grouped as responders and non-responders regardless of treatment and the average PRCQ or Degree of Relief of IBS Symptoms score was calculated for each group. The potential PRCQ and Degree of Relief of IBS symptom scores were categorized as follows:

- 1.0-1.49 = Completely relieved,
- 1.5-2.49 = Considerably relieved,
- 2.5-3.49 = Somewhat relieved,
- 3.5-4.49 = Unchanged,
- 4.5-5.49 = Somewhat worse,
- 5.5-6.49 = Considerably worse, and
- 6.5-7.0 = As bad as I can imagine.

If the primary efficacy parameter responder definition is clinically meaningful, one would expect the average score of the responder group to map to “Somewhat relieved” or better (i.e., a score of 3.49 or less) while nonresponders would be expected to have received little or no relief of their symptoms (i.e., a score of 3.5 or higher).

The patients who were responders had an average PRCQ score corresponding to “Considerably relieved” for most parameters and “Somewhat relieved” for the 9/12 Abdominal Pain responder as assessed by the single overall Degree of Relief of IBS Symptoms question. In contrast, the average scores for each of the nonresponder groups were at least 1 full point higher (i.e., less relief) than their corresponding responder group, with scores categorized as “Unchanged” for most groups and “Somewhat relieved” for the 9/12 Week APC 3 + 1 responder and 9/12 Week CSBM 3 + 1 responder (for the Degree of Relief of IBS Symptoms question only). See Table 41.

Table 41: PRCQ and Degree of Relief Treatment Period Averages for the Primary Efficacy Parameters

<i>Primary Parameter</i>	<i>PRCQ Average (SD)</i>	<i>Degree of Relief of IBS Symptoms Average (SD)</i>
9/12 Week APC 3 + 1		
Responder	1.8(0.6) 1.9(0.5) ^a _b	1.9 (0.5)
Nonresponder	3.4(1.0) ^a 3.3(1.0) ^b	3.3 (0.9)
9/12 Week CSBM 3 + 1		
Responder	2.0(0.7)	2.1 (0.6)
Nonresponder	3.5(1.0)	3.3 (0.9)
9/12 Week Abdominal Pain		
Responder	2.4(0.7)	2.5 (0.7)
Nonresponder	3.5(0.9)	3.5 (0.9)
6/12 Week APC +1		
Responder	3(0.27) ^a 2.3(0.6) ^b	2.3 (0.6)
Nonresponder	3.6(0.9) ^a 3.5(0.9) ^b	3.5 (0.8)

Treatment Period average intervals for the anchors are 1.0-1.49 = completely relieved, 1.5-2.49 = considerably relieved, 2.5-3.49 = somewhat relieved, 3.5-4.49 = unchanged, 4.5-5.49 = somewhat worse, 5.5-6.49 = considerably worse, and 6.5-7.0 = as bad as I can imagine

- a. PRCQ CSBM Frequency
- b. PRCQ Abdominal Pain

6.1.7 Subpopulations

Medical Officers Comments:

The subgroup analysis of the pooled data shows that this drug appears to be effective in all subgroups including in the male population. All the other drugs approved for IBS in recent years have been approved for women only. Lotronex (alosetron) and Tegaserod (Zelnorm) was limited to use in women secondary to safety concerns and the desire to limit exposure to those most likely to benefit. Lubiprostone (Amitiza) was approved for use in women only because the low enrollment of men did not allow the p-value of the primary endpoint to reach statistical significance. However, linaclotide does show efficacy in the male population with trends towards efficacy in each of the four primary endpoints and reaches statistical significance in the 9/12 week combined endpoint and

the 9/12 week CSBM 3+1 endpoint (See figure Figure 16 on page 107). While only ~10% of the population was male this is consistent with the incidence of IBS in the general population in the US. In addition, linaclotide shows statistically significant efficacy in the CIC population at both doses in both men and women (see clinical review of CIC initiation by Erica Wynn, MD). Therefore, this reviewer would recommend approval of linaclotide in both males and females.

A comparison of the efficacy results in subpopulations was performed on the IBS-C Phase 3 Pooled ITT Population data. The subpopulations for these analyses were:

- Age (< 65, ≥ 65, > 65 to < 75, and ≥ 75 years),
- Sex (male and female),
- Race (Black, Caucasian, and Other Races),
- Ethnicity (Hispanic or Non-Hispanic), and
- BMI (< 30 kg/m² or ≥ 30 kg/m²)

The age < 65 and age ≥ 65 years subpopulations included 1517 and 85 patients, respectively. For the four Phase 3 primary efficacy parameters, the odds ratios show that improvements were observed for linaclotide in patients < 65 and those ≥ 65 years. Although the responder rates in patients ≥ 65 for the primary efficacy parameters, as well as for the secondary responder efficacy parameters, were similar to, or even higher than, the corresponding responder rates in the younger patients, the placebo rates in the older group were notably higher resulting in a slightly lower difference from placebo in patients ≥ 65 compared to patients < 65.

Improvements in the change-from-baseline secondary abdominal-symptom parameters (Abdominal Pain, Abdominal Discomfort, Bloating, and Percent Abdominal Pain-free Days) were observed for linaclotide versus placebo in patients < 65 and those ≥ 65 years and were similar across the two subpopulations ($p \leq 0.05$ for linaclotide versus placebo for each efficacy parameter in both subpopulations except for Percent of Abdominal Pain-free Days in patients ≥ 65 years old).

Improvements in the change-from-baseline secondary bowel-symptom parameters (CSBMs, SBMs, Stool Consistency, and Severity of Straining) were demonstrated with linaclotide versus placebo for both age subpopulations ($p \leq 0.05$ for each parameter for linaclotide versus placebo in both subpopulations).

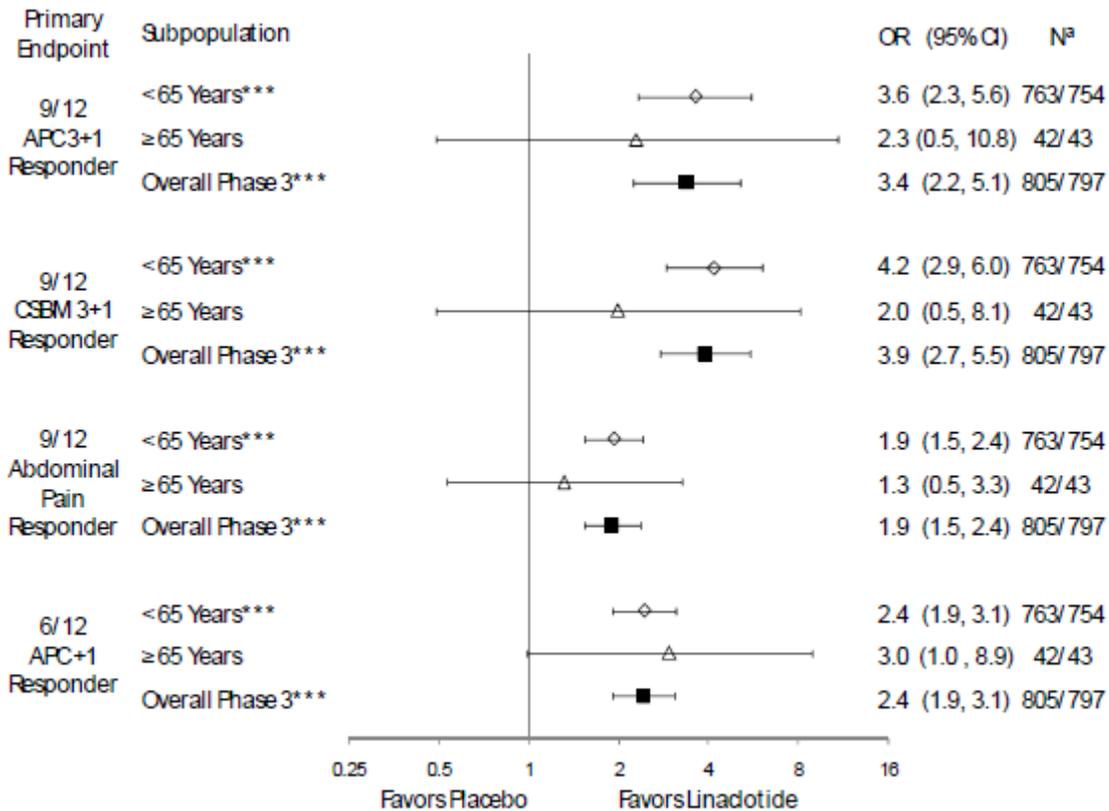
The results for the primary and secondary efficacy parameters were also summarized using 3 age groups: <65, ≥ 65 and < 75, and ≥ 75 years old. The observed treatment effects were generally similar across the 3 age subpopulations.

See discussion in

Figure 15: Phase 3 Primary Efficacy Parameters by Age (IBS-C Phase 3 Pooled ITT Population) on page 106, and

Figure 16: Phase 3 Primary Efficacy Parameters by Sex (IBS-C Phase 3 Pooled ITT Population) on page 107, and
 Figure 17: Phase 3 Primary Efficacy Parameters by Race (IBS-C Phase 3 Pooled ITT Population) on page 108.

Figure 15: Phase 3 Primary Efficacy Parameters by Age (IBS-C Phase 3 Pooled ITT Population)



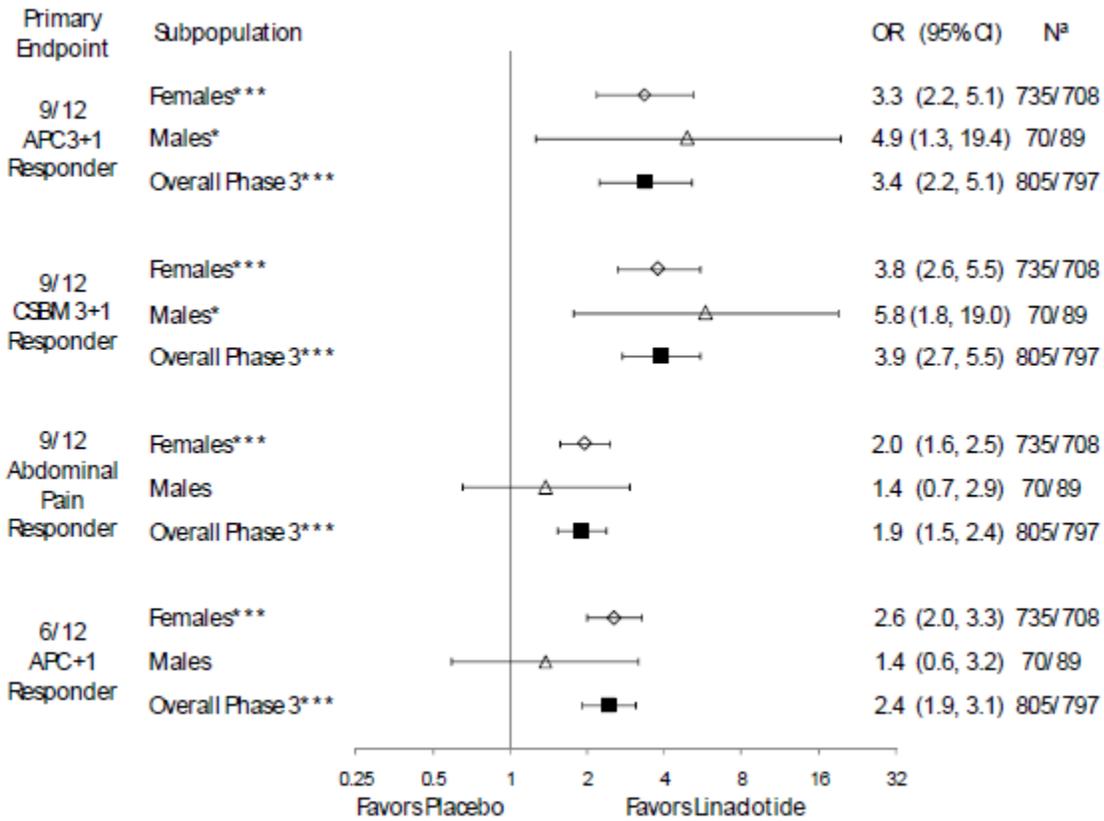
*** p < 0.0001

p-value, OR, and 95% CI are obtained from the CMH tests controlling for trial and geographic region.

OR = odds ratio; CI = confidence interval

a. 290 ug linaclotide group/placebo group; ITT Population is presented.

Figure 16: Phase 3 Primary Efficacy Parameters by Sex (IBS-C Phase 3 Pooled ITT Population)



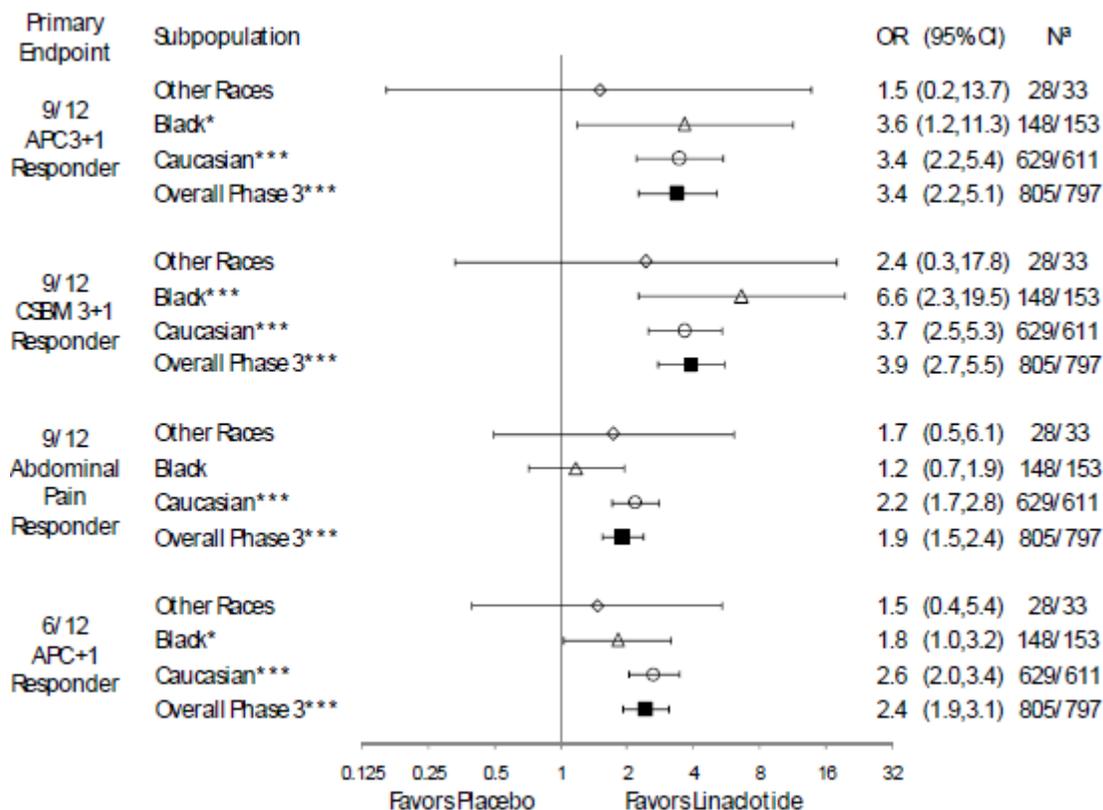
* p ≤ 0.05; *** p < 0.0001

p-value, OR, and 95% CI are obtained from the CMH tests controlling for trial and geographic region.

OR = odds ratio; CI = confidence interval

a. 290 ug linaclootide group/placebo group; ITT Population is presented.

Figure 17: Phase 3 Primary Efficacy Parameters by Race (IBS-C Phase 3 Pooled ITT Population)



6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations – Review of Dose Ranging Trials

Medical Officer’s Comments:

The applicant performed placebo controlled trials with only the higher dose (290µg) of linaclotide; however, dose reductions to 145µg were allowed in IBS-C patients in the long-term trials. Overall 15% of patients in these trials tolerated the lower dose, and remained on linaclotide long-term. Adverse events of diarrhea occurred with approximately equal frequency in both doses in the controlled trials with chronic constipation patients. The phase 2 trials showed a dose response relationship for diarrhea AEs.

The conclusion would be that some patients, who have diarrhea from linaclotide, may benefit from a trial of the 145µg dose.

Dose Ranging Phase 2B Trials in IBS-C

Medical Officer's Comments:

Linaclotide demonstrated therapeutic efficacy in relieving constipation in IBS-C as demonstrated by improvements over baseline in the primary efficacy endpoint and various other secondary and exploratory endpoints in this dose ranging trial. The applicant elected to pursue the 290ug dose as the primary dose for phase 3 trials as they felt it showed the most favorable risk-benefit profile. However, clear dose-related trends for efficacy were not noted in this study. A trend toward increasing AE's, especially diarrhea, was noted with the 600µg dose.

A plasma concentration-response relationship cannot be determined for linaclotide due to the limited systemic absorption of linaclotide (See discussion in See 4.4 Clinical Pharmacology on page 29. Therefore, in the absence of clinical pharmacology guidance or biomarkers, dose selection and recommendations are based entirely on clinical results.

See discussion in Section 7.5.1 Dose Dependency for Adverse Events on page 194.

The linaclotide dose of 290 ug was chosen for the phase 3 IBS-C trials based on the safety and efficacy results from study MCP-103-202, the phase 2b 12-week dose-range-finding study in patients with IBS-C (See Table 42). This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled, dose-range-finding oral dose study of 75, 150, 300, and 600 µg linaclotide. Approximately 80 patients were randomized per group. The primary efficacy endpoint in this study was the change from Pretreatment Period (baseline) in weekly normalized Complete Spontaneous Bowel Movement (CSBM) Rate during the 12-week Treatment Period.

Most changes in efficacy endpoints were statistically significant relative to placebo, especially for the two highest doses evaluated. In this study, the 300 µg dose of linaclotide consistently provided greater response for the IBS-C endpoints, compared to the lower doses (75 ug, 150 µg) or even the highest dose (600 µg) evaluated in this study. For the primary endpoint (CSBM rates) and two key secondary endpoints (CSBM/SBM 75% responders), the 75 µg dose provided better outcomes compared to the 150 µg and 600 µg doses of linaclotide. For most other secondary endpoints, the efficacy findings were comparable for the 75 and 150 µg doses but still numerically smaller compared to either the 300 or 600 µg. Thus a clear dose-response for efficacy endpoints was not noted in this phase 2b trial for linaclotide in IBS-C.

Improvement over baseline in the various primary and secondary endpoints was seen as early as week 1 and effects were sustained throughout the 12 week treatment period. Following cessation of therapy, values returned toward baseline without worsening (rebound) of symptoms.

There was also evidence that the incidence of diarrhea reported as an AE, as well as dropouts due to AEs of diarrhea, increased with increasing linaclotide dose.

Summary of dose response in phase 2 dose ranging trials and phase 3 trials in Chronic Idiopathic Constipation (CIC)

Medical Officers Comments:

In the phase 2B trial a dose-response trend was noted for several of the efficacy endpoints. However, no trend for dose-response was noted for the two doses in the phase 3 trials. The phase 3 trials were not powered to demonstrate difference between the two doses. There is no overall increase in the frequency of AE's at the 300 µg dose compared to 150 µg dose of linaclotide; however the frequency of diarrhea may be more at the higher dose. In addition, diarrhea related discontinuations, as well as incidence of severe cases of diarrhea was slightly higher at the higher doses, though not consistently across CIC studies.

The following is summarized from clinical pharmacology review by Sandhya Apparaju, Ph.D:

“In the phase 2B dose ranging trials, linaclotide demonstrated therapeutic efficacy in relieving constipation as demonstrated by improvements over baseline in the various primary and secondary efficacy endpoints. The 600 µg dose exhibited the highest incidence of total and specific AEs, including discontinuation due to AEs. The percentage of diarrhea, headache and abdominal pain was noted at a higher frequency at the 300µg dose compared to lower doses.

Statistically significant changes from baseline relative to placebo were noted for most primary and secondary endpoints at all doses evaluated in these studies. Statistical significance was noted in the weekly response outcomes relative to placebo and the effect was generally achieved within the first week of dosing and sustained throughout the double-blind treatment period. Withdrawal of linaclotide did not appear to result in worsening (rebound) of baseline symptoms during the 2 to 4 week randomized withdrawal period.

Dose-related trends for efficacy were noted for several endpoints over the dose range investigated in the phase 2b study (75 – 600µg) and during the phase 3 trial LIN-MD-01 that evaluated two doses of linaclotide (150 and 300µg).

Incidence of diarrhea varied with linaclotide dose with the lowest incidence (4.8%) occurring in the 300 µg dose group and the highest incidence (14.3%) occurring in the 600 µg dose group in the phase 2B trial. There was also a dose-related increase in the number of patients who discontinued study drug due to diarrhea. In the phase 3 trials in which two doses (145 µg and 290 µg) were evaluated, in general, the incidence of diarrhea, nausea, abdominal pain and headache were highest in the 290 µg dose group, although the difference between the two groups was not marked.”

**Table 42: Change from Baseline in Bowel Habits and IBS-C Symptoms (ITT Population, N=419)
Phase 2B Trials in IBS-C**

Endpoint ^a	Placebo (n=85)	Linaclotide			
		75 ug (n=79)	150 ug (n=82)	300 ug (n=84)	600 ug (n=89)
CSBM Frequency ^b (CSBM/week)	1.01	2.90**	2.49*	3.61***	2.68**
CSBM 75% Responder ^c	11.8%	25.3%*	19.5%	32.1%**	23.6%*
SBM Frequency ^b (SBM/week)	1.68	4.62***	4.36***	4.97***	5.64***
SBM 75% Responder ^c	29.4%	54.4%*	39.0%	65.5%***	52.8%*
Stool Consistency (7-point ordinal BSFS ^d)	0.56	1.91***	1.80***	2.28***	2.20***
Straining ^e (5-point ordinal scale)	-0.71	-1.23***	-1.20***	-1.48***	-1.35***
Abdominal Pain ^f (5-point ordinal scale)	-0.49	-0.71*	-0.71*	-0.90***	-0.86**
Abdominal Discomfort ^f (5-point ordinal scale)	-0.45	- 0.6 5	-0.68*	-0.90***	-0.81**
Bloating ^f (5-point ordinal scale)	-0.38	-0.64*	- 0.59	-0.88***	-0.75**
Degree of Relief of IBS Symptoms ^g (7-point balanced scale)	-0.81	-1.33**	-1.37**	-1.66***	-1.49***
Adequate Relief IBS Symptoms 50% Responder	29.4%	50.6%*	51.2%*	67.9%***	62.9%***
Adequate Relief IBS Symptoms 75% Responder (>75% of 12 wks)	22.4%	38.0%*	32.9%	51.2%**	42.7%*
Average IBS Severity ^e (5-point ordinal scale)	-0.56	-0.87*	-0.88*	-1.08**	-1.02**

Constipation Severity ^e (5-point ordinal scale)	-0.65	-1.09**	-1.04*	-1.42***	-1.23***
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p-values: * \square 0.05, ** $<$ 0.001, *** $<$ 0.0001

a. The values for responder endpoints are percentages with p-values obtained from CMH tests with each linaclotide group tested pairwise versus the placebo group. The values for the other endpoints are the change from baseline (presented using least-square means) with p-values obtained from an ANCOVA model that had fixed effects for treatment group and study center (pooled by geographic region) and the Pretreatment Period (baseline) value as a covariate.

b. An SBM is a BM that occurs in the absence of laxative, enema, or suppository use during the preceding 24 hours; a CSBM is an SBM associated with a sensation of complete emptying of the bowels.

c. A (C)SBM 75% Responder had IVRS data for \square 4 days/week and an average (C)SBM rate \square 3/week and increased by \square 1 from Pretreatment Period (baseline) for 9 of 12 Treatment Period weeks.

d. BSFS stool consistency scale: 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, a mushy stool; 7=watery, no solid pieces (entirely liquid).

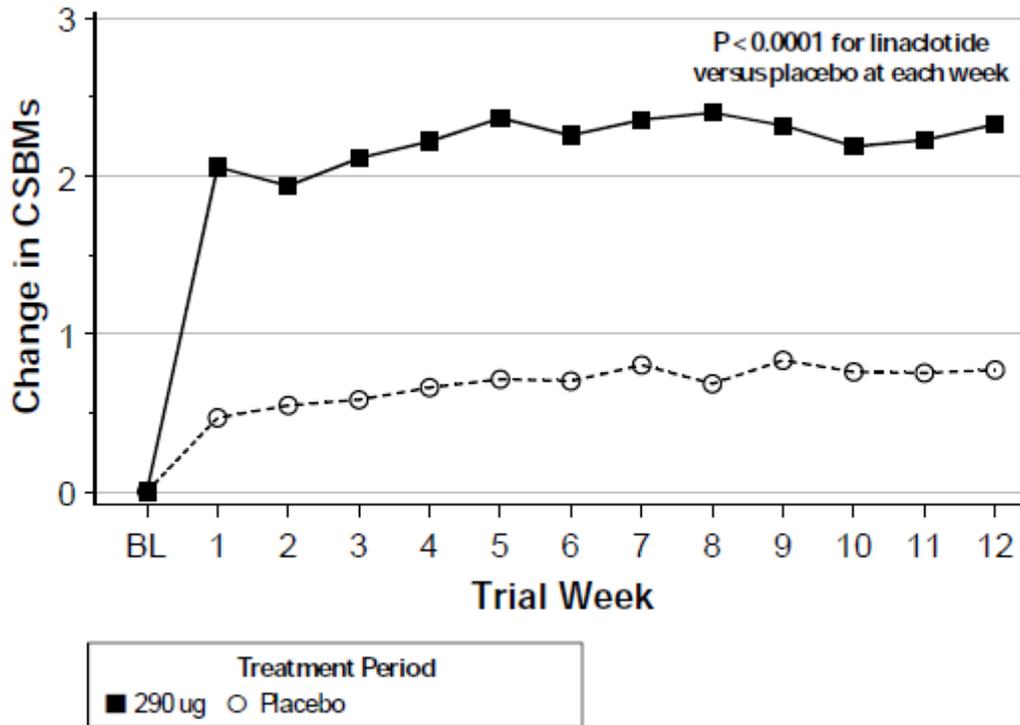
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Medical Officer's Comments:

The 26 week trial did show persistence of efficacy through out the length of the trial and no evidence of tolerance. However, for this exploratory endpoint it is not known how much of an increase over baseline is clinically meaningful to patients.

Figure 18: LS Mean Changes from Baseline in CSBM Frequency Rate by Week (IBS-C Phase 3 Pooled ITT Population) presents the LS mean change from baseline in weekly CSBM Frequency Rate for the IBS-C Phase 3 Pooled ITT Population. For Weeks 1 through 12, patients on the 290ug linaclotide dose showed an increase in the CSBM Frequency Rate compared with placebo ($p < 0.0001$).

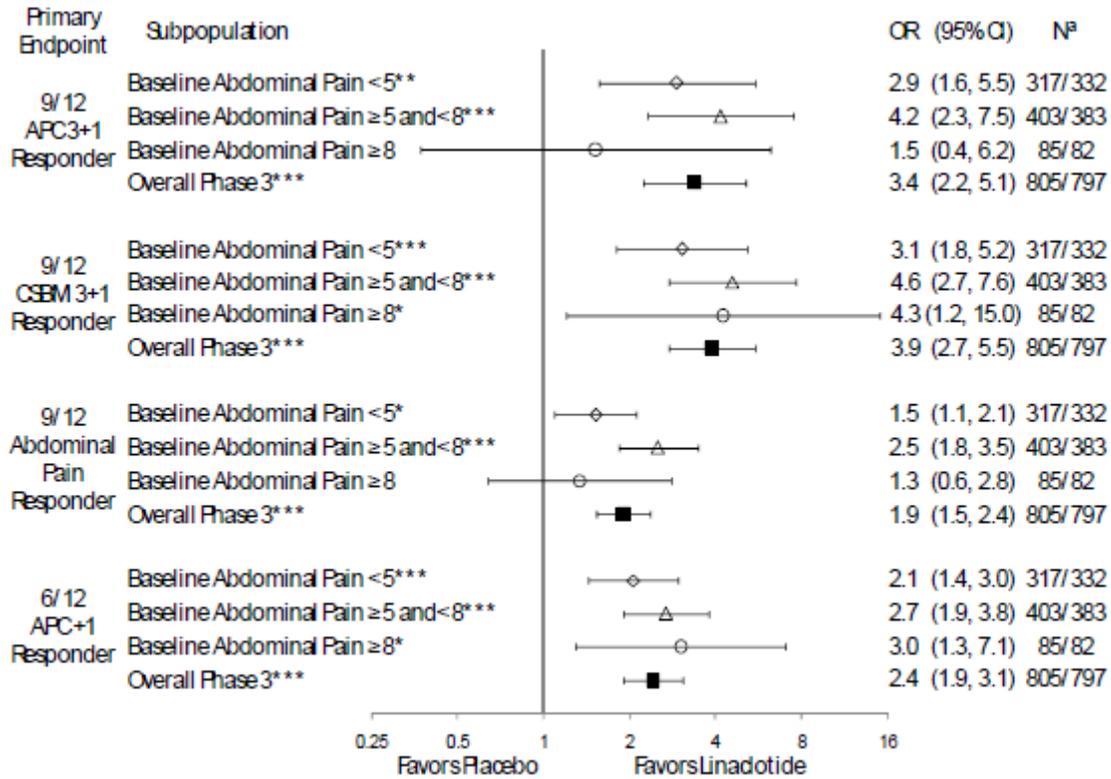
Figure 18: LS Mean Changes from Baseline in CSBM Frequency Rate by Week (IBS-C Phase 3 Pooled ITT Population)



p-values are based on a comparison of linaclotide versus placebo in an ANCOVA model with treatment group, trial, and geographic region as factors and baseline value as covariate

The Abdominal Pain < 5, Abdominal Pain ≥ 5 and < 8, and Abdominal Pain ≥ 8 at baseline subpopulations included 649, 786 and 167 patients, respectively. These disease severity subgroups were defined by distributing into thirds the range of eligible average baseline scores of 3 to 10 on the 11-point Abdominal Pain at its Worst scale. For the four phase 3 primary efficacy parameters and for the two phase 3 secondary responder parameters, the odds ratios show that improvements were observed for linaclotide in all 3 Abdominal Pain subpopulations.

Figure 19: Phase 3 Primary Efficacy Parameters by Baseline Abdominal Pain (IBS-C Phase 3 Pooled ITT Population)



* p ≤ 0.05; ** p < 0.001; *** p < 0.0001
 p-value, OR, and 95% CI are obtained from the CMH tests controlling for trial and geographic region.
 OR = odds ratio; CI = confidence interval
 a. 290 ug linaclotide group/placebo group; ITT Population is presented.

6.1.10 Additional Efficacy Issues/Analyses

See also discussion of dose reductions in Section 7.2.2 Explorations for Dose Response on page 130

7 Review of Safety – IBS-C and CIC - Combined Indications

Safety Summary

The safety of linaclotide for both the Irritable Bowel Syndrome with Constipation (IBS-C) indication and the Chronic Constipation (CIC) indication was established by reviewing the data from all patients receiving linaclotide in two phase 2 dose ranging trials, four phase 3 placebo-controlled trials, and two open label long-term safety trials, as well as some additional patients in phase 1 trials.

Preclinical data generally reported no significant safety signals except for deaths in very young mice at a low dose (See discussion in Section 4.3 Nonclinical Pharmacology/Toxicology on page 27. Because of this safety signal linaclotide will be contraindicated in all children until such time that more information can be obtained. The Division will require a post-marketing studies to gather more data on the mechanism of these deaths and its relevance to humans. The pediatric development plan will be placed on deferral until the Division can evaluate the results of the studies, except for the development of the PRO instrument for IBS in children which can be initiated (See discussion in Section 2.5.2 Pediatric on page 16).

Because linaclotide is a small peptide that is broken down in the gastrointestinal (GI) tract, it has very low systemic exposures, and the overall safety profile appears to be good. The majority of adverse events (AE's) occur in the GI tract. There is very little difference between the safety profile of linaclotide in CIC and IBS-C patients.

The phase 2 dose ranging trials did not show a clear dose response relationship between the 145 µg and 290 µg doses, but did show a trend toward higher incidence of diarrhea and other AE's with increasing doses. The placebo-controlled trials tested two doses of linaclotide for CIC, 145 µg and 290 µg, but only one dose, 290 µg for IBS-C patients. The long-term safety trials, started all patients on the 290 µg dose, but allowed dose reductions to 145 µg for AE's. Exposures were adequate with over 4,000 patients exposed, and over 400 of each CIC and IBS-C patients were treated with linaclotide in the double-blind trials.

There were 7 deaths, none were judged to be drug related. There was a higher incidence of discontinuations in the treatment arm (8.5%) than in the placebo arm (3.4%) in the controlled trials. The majority of these were secondary to diarrhea (4.8% of the trial population), however there was no significant difference in incidence of diarrhea or GI AE's between the two doses in the CIC trials. In the long term safety trials AE's resulting in discontinuations occurred in 10.2% of patients, with 4.9% of the trial population,, secondary to diarrhea. Discontinuations were similar between indications.

Serious AE incidence was equal between groups in the placebo-controlled trials, and the applicant reported no SAE's of diarrhea. However there was one patient in the long-term safety trials, with CIC who had an SAE of dehydration and orthostatic hypotension who also had diarrhea, nausea and vomiting. The episode was reported as drug related by the Investigator. There were a few other cases of orthostatic hypotension and dehydration; however none of the other cases were reported as Serious AEs.

Adverse Events occurred most commonly in the GI SOC, the most common AE is diarrhea, occurring in approximately 17% of treated patients in the placebo-controlled trials, and in more than 30% of patients in the long-term trials.

Dose reduction, from 290µg to 145µg occurred in more than 30% of patients in the long term, open-label trials, most of these were in the GI SOC, most of which were reported as diarrhea. One-half of the patients in the dose-reduced group were able to tolerate the lower dose and complete the trial; half of the patients in this group eventually discontinued treatment.

There was not a significant difference in AE's or diarrhea incidence or severity between the two doses of linaclotide used in the CIC patients. However, in the phase 2 trials, there was evidence of increase GI AE's with increasing dose. Diarrhea occurred more commonly in patients >65 years of age (~5% greater than younger patients). Only one Serious AE was reported in association with diarrhea. Severe diarrhea was reported in 2-3% of patients. Diarrhea occurred most commonly in the first 2 to 4 weeks of treatment.

Because of the history of Ischemic Colitis (IC) with other IBS drugs, we were diligent in examining for cases. Three cases were identified, all in high risk patients, and all resolved. No other cases were identified. The conclusion of this reviewer is that there does not appear to be an association with linaclotide and no safety signal of IC was identified in this safety dataset. Because of the prior history with IC appearing post marketing in other IBS drugs, post-marketing surveillance and reporting of any cases of ischemic colitis is recommended. Additionally, recommendation is made to include language in the labeling to remind patients to seek immediate medical evaluation for severe abdominal pain or bloody diarrhea because the adverse events associated with linaclotide included diarrhea and hematochezia (the latter seen in both placebo and the linaclotide arms) and because abdominal pain is a manifestation of IBS-C. The goal of this labeling language will be to be sure that patients and clinicians don't ignore the signs of IC or other symptoms of serious pathology.

The risk for immunogenicity appears to be low in the small peptide that is broken down in the GI tract, and no safety signal of anaphylactic reactions or associated allergic reactions were identified.

There is no evidence of rebound or withdrawal effect, however patients return to baseline symptoms rapidly after linaclotide withdrawal.

In conclusion, linaclotide appears to have a favorable safety profile with diarrhea being the most common AE, with rare occurrences of Serious Adverse Events of diarrhea and a severe diarrhea incidence of 2 to 3 %.

7.1 Methods

Statistical analyses were performed using version 9.2 of SAS on a UNIX operating system. See SAP and statistical review by Dr Milton Fann for complete analysis of methods.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

For the purpose of the ISS, a total of 13 clinical studies (six phase 3, four phase 2, and three phase 1) with linaclotide have been organized into dataset groups based on study phase, study population, and study design:

Group 1 (Phase 3 placebo-controlled trials) consists of four phase 3, double-blind, placebo-controlled trials. Data are integrated for CIC trials, IBS-C trials, and for the combined CIC and IBS-C trials:

- LIN-MD-01 in patients with CIC (12 weeks of double-blind treatment)
- MCP-103-303 in patients with CIC (12 weeks of double-blind treatment)
- LIN-MD-31 in patients with IBS-C (12 weeks of double-blind treatment)
- MCP-103-302 in patients with IBS-C (26 weeks of double-blind treatment)

The LIN-MD-31 and MCP-103-303 protocols also included 4-week Randomized Withdrawal (RW) Periods. Safety data from the RW Periods are not integrated in Group 1 analyses, but are presented separately by study. Data from the patients who were treated with linaclotide in the RW Period are summarized in the Group 4 analyses (see below).

Group 2 (Phase 2 CIC studies) consists of two phase 2, double-blind, placebo-controlled CIC studies:

- Study MCP-103-004 (2 weeks of double-blind treatment)

- Study MCP-103-201 (4 weeks of double-blind treatment).

Data from the two Phase 2 IBS-C studies were not integrated due to their different treatment durations (MCP-103-005 = 5 days, MCP-103-202 = 12 weeks). Data from these 2 studies are however, presented separately in this document within sections summarizing Group 2 (Phase 2 CIC) study data. Also, key safety data are included in integrated analyses as part of Group 4 (see below).

Group 3 (Long-term safety [LTS] studies) consists of the two phase 3, open-label LTS studies:

- MCP-103-305. This study recruited patients who had completed MCP-103-303, MCP-103-302 or any Phase 2 study; these patients were “rollover” (RO) patients. In addition, patients who were ineligible to take part in MCP-103-303 or MCP-103-302, but who fulfilled the criteria for the LTS study were also enrolled; these patients were “randomization-ineligible” (RI) patients.
- LIN-MD-02. This study included RO and RI patients from the phase 3 trials LIN-MD-01 and LIN-MD-31, as well as RO patients from any Phase 2 study.

RI patients are patients who completed the Pretreatment Period (including the safety procedures at the Screening and Randomization Visit) of one of the four Phase 3 efficacy trials but were not randomized for reasons not related to their classification as having CIC or IBS-C by Rome II criteria. In contrast, RO patients were randomized and completed a Phase 2 or 3 placebo-controlled lead-in study.

For the RO patients, data from a lead-in study were not included in the presentation for this group, which was limited to the exposure and safety data obtained following a patient’s entry into the LTS study. Each LTS study enrolled both CIC and IBS-C patients.

The LTS studies of Group 3 (LIN-MD-02 and MCP-103-305) are currently ongoing. Therefore, all analyses that are presented in the ISS are based on data (up to the cutoff date of 11-Oct-2010) that are pooled across studies; no analyses are presented for individual studies.

Group 4 (all-linaclotide) includes the pooled data from all patients while they were receiving linaclotide (Phase 2 and 3 only). Exposure for Group 4 was summarized for the linaclotide treatment periods in Phase 2 and 3 studies, but excluded the Phase 2 lead-in study exposure of the RO patients. Safety data for Group 4 were collected upon a patient’s first exposure to linaclotide so that data from a lead-in study for the RO patients were included in the presentation. If a patient from trial LIN-MD-31 or MCP-103-303 was randomized to placebo and then allocated to linaclotide treatment during

the RW Period, the safety data during the RW Period were included in the Group 4 summaries. If a patient from trial LIN-MD-31 or MCP-103-303 was randomized to linaclotide and then rerandomized to placebo treatment during the RW Period, the safety data during the RW Period were not presented in the Group 4 summaries. Only the linaclotide-treatment (not placebo-treatment) periods were included.

Group 4S is a subset of Group 4 and includes pooled data from all patients while they were receiving linaclotide, but does not include data from Phase 2 studies. Group 4S combines the linaclotide-treated patients in Group 1 and Group 3, but does not include patients from Group 2 who did not rollover into an LTS study. Group 4S was established at the request of the FDA at the 22-Mar-2011 Pre-NDA meeting (see SAP Amendment 2 in Appendix I). The analyses on the Group 4S data are displayed by subgroup: Phase 3 RO patients, “other” Phase 3 patients, total Phase 3 patients, Phase 2 RO patients, RI patients, and all patients combined. The “other” Phase 3 patients group consists of patients who received only placebo in a Phase 3 double-blind trial followed by linaclotide treatment in an LTS study or who received linaclotide in a Phase 3 double blind trial only without enrolling in an LTS study.

Group 5 (Phase 1 studies) consists of three Phase 1 clinical pharmacology studies, which enrolled healthy subjects:

- MCP-103-001 (single-ascending-dose study)
- MCP-103-002 (multiple-ascending-dose study, 7 days of double-blind treatment)
- MCP-103-103 (food-effect study, 15 days of double-blind treatment)

Given the small number of subjects in the three Phase 1 studies, safety information from these studies is presented separately by study and not pooled.

A pooled database consisting of the 10 Phase 2/3 studies includes the following patient information: exposure to investigational product, demographics and other baseline characteristics, concomitant medications, treatment-emergent adverse events (TEAEs), deaths, serious adverse events (SAEs), adverse events leading to dropout (ADOs), clinical laboratory parameters, vital signs, and electrocardiogram (ECG) parameters.

Of the six phase 3 studies, two are ongoing open-label LTS studies, for which safety information continues to be collected. For these two studies, the safety information summarized in this section was collected up to and including the cut-off date of 11-Oct-2010.

The 120-day safety update will be analyzed in 7.7 Additional Submissions / Safety Issues on page 210.

Medical Officer's Comments:

Each section of the Safety Review focuses on the most appropriate datasets for assessing the safety of linaclotide. This review will focus mostly on the analysis of group 1 (the placebo controlled phase 3 trials) and Group 3 (all linaclotide exposed patients); however, other groups will be included when the data are meaningful to the analysis.

7.1.2 Categorization of Adverse Events

For the phase 3 RI patients and the phase 2 RO patients in Group 3, a TEAE was defined as an AE that started after the first dose of open-label investigational product or started before the day of the first dose of open-label investigational product but increased in severity afterwards. If more than 1 AE with the same preferred term was reported before the day of the first dose of open-label investigational product, the AE with the greatest severity was used as the benchmark for comparison with the AEs occurring during the LTS study that were also coded to that preferred term. An AE that occurred more than 1 day after the day of the last dose of the open-label investigational product in an LTS study was not counted as a TEAE.

The number and percentage of patients with TEAEs were summarized by system organ class (SOC) and preferred term for each study Group, and for the relevant demographic subgroups (i.e., sex, age group, race, ethnicity, and BMI) in Group 1.

For Group 1 and Group 3, the number and percentage of patients with TEAEs were tabulated by SOC and severity; and by SOC and relationship to investigational product. If more than 1 event occurred during the study with the same preferred term for the same patient, the patient was counted only once for that preferred term using the most severe occurrence for the summarization by severity and using the most related occurrence for the summarization by relationship to the investigational product.

For Group 1 patients who prematurely discontinued from the Phase 3 double-blind trials due to “Lost to Follow-up” or “Withdrawal of Consent”, the number and percentage of patients with TEAEs that were still ongoing at the time of premature discontinuation were summarized by SOC and preferred term.

Also, for Group 1 the TEAEs were summarized by SOC and preferred term and by AE onset time as follows: 0 to 4, 4 to 12, and > 12 weeks from the date of the first dose of the double-blind investigational product.

For Group 4S, TEAEs were also summarized by SOC and preferred term according to AE onset time for the entire continuous-linaclotide-exposure period and the following continuous-linaclotide exposure intervals: > 0 day and ≤ 3 months, > 3 months and ≤ 6 months, > 6 months and ≤ 9 months, > 9 months and ≤ 12 months, and > 12 months. In the summary of each exposure interval, a patient who had a continuous-linaclotide exposure equal to or less than the lower bound of the exposure interval was excluded.

The severity of AEs as judged by the Investigator was based on the following criteria:

- Mild: The AE was an annoyance to the patient but did not further hinder baseline functioning; the AE may have been intermittent or continuous
- Moderate: The AE caused the patient to experience some discomfort or some interference with normal activities but was not hazardous to health; prescription drug therapy may have been employed to treat the AE
- Severe: The AE caused the patient to experience severe discomfort or severely limited or prevented normal activities and represented a definite hazard to health; prescription drug therapy and/or hospitalization may have been employed to treat the AE

The potential relationship of AEs to treatment based on the Investigator's judgment is categorized as follows:

- Unrelated: Event could be fully explained by the patient's clinical state or other agents/therapies
- Unlikely: Event was most likely explained by the patient's clinical state or other agents/therapies
- Possible: Event may have been explained by administration of the investigational product or by the patient's clinical state or other agents/therapies
- Probable: Event was most likely explained by administration of the investigational product rather than the patient's clinical state or other agents/therapies
- Definite: Event could have been fully explained by administration of the investigational product

The above categories were dichotomized as Not Related (unrelated or unlikely on the AE eCRF) and Related (possible, probable or definite on the AE eCRF).

Version 13.0 of the *Medical Dictionary for Regulatory Activities* (MedDRA) was used for coding AEs across all studies in Groups 1 and 2 (the double-blind, placebo-controlled studies), Group 3 (the open-label LTS studies), and IBS-C studies MCP-103-202 and MCP-103-005. For any studies in which AEs were coded with an older version of MedDRA, the AEs were recoded using the current Version 13.0 of MedDRA.

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

Collectively, Groups 1, 2, and 3 provide data on all patients in the linaclotide program. Group 4 contains longitudinal data on all linaclotide-treated patients (i.e., no placebo data are included); these data are used to present total patient exposure to linaclotide. Group 4S, which does not include phase 2 data, was requested by the FDA, and is used for presentation of all other results. Group 5 is not included because healthy volunteer data were not pooled for the ISS and the results can be obtained from the individual Phase 1 clinical study reports (CSRs).

The Safety Populations of Groups 1, 2, and 3 consist of all patients who have taken at least 1 dose of investigational product during the Treatment Period of studies in Groups 1, 2, and 3, respectively. The Safety Population of Group 4 and Group 4S consists of all patients who have taken at least 1 dose of linaclotide during the Treatment Period or the RW Period of studies in Group 4 or Group 4S. All safety data were summarized based on the Safety Population, using descriptive statistics, unless otherwise specified.

Duplicate Patients

In the Phase 3 clinical program, there were 25 cases of patients who enrolled more than once, either in the same study or in multiple Phase 2/3 studies in violation of entry criteria. These 25 patients will be referred to as “duplicate patients”

Table 43: Rules for Inclusion of Data from Duplicate Patients in the ISS Pooled Summaries

ISS Group	Data Inclusion in the Pooled-by-Indication Summary	Data Inclusion in the Overall (CIC + IBS-C)-Pooled Summary
Group 1	Patient data from the first phase 3 trial in each indication	Patient data from the first phase 3 trial, regardless of indication (CIC or IBS-C)
Group 2 ^a	Patient data from the Phase 2 CIC studies for the CIC indication summary; not applicable for the IBS-C indication summary	Not applicable
Group 3	Patient data from the first LTS study in each indication into which a duplicate patient rolled over from a preceding Phase 3 trial (or a Phase 2 study if the patient was not in a preceding Phase 3 trial); if the patient was not a roll-over patient, data from the first LTS study in each indication that the patient entered after being randomization ineligible in a Phase 3 trial	Patient data from the first LTS study, regardless of indication, into which a duplicate patient rolled over from a preceding Phase 3 trial (or a Phase 2 study if the patient was not in a preceding Phase 3 trial); if the patient was not a roll-over patient,, data from the first LTS study, regardless of indication, that the patient entered after being randomization-ineligible in a Phase 3 trial
Group 4	Patient data for each indication from the Phase 3 trial (if any) and the LTS study (if any) that were included in the ISS Group 1 and Group 3 pooled-by-indication summary, along with data from the Phase 2 study for that indication (if any); only data in the linaclotide-treatment periods in the studies were included	Patient data from the Phase 3 trial (if any) and the LTS study (if any) that were included in the ISS Group 1 and Group 3 overall-pooled summary along with data from the Phase 2 study (if any); only data in the linaclotide-treatment periods in the studies were included

^a In Group 2, the safety data from the Phase 2b IBS-C Study MCP-103-202 was summarized separately. ISS = Integrated Summary of Safety; LTS = long-term safety.

7.2 Adequacy of Safety Assessments

The Applicants safety evaluation with the addition of the responses to the Information Requests made by the Division is adequate.

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

Medical Officer's Comments:

The exposures meet the Agency requirements for exposures of chronic drugs, and is acceptable.

The investigational product doses (30, 75, 100, 150, 300, 600, 1000, and 3000 ug) specified in the study protocols represent the total peptide content in each capsule. For all Phase 2/3 studies except for study MCP-103-004 and MCP-103-005, newly improved analytical methods have shown that 75, 100, 150, 300, 600, and 1000 ug of total peptide content correspond to 72, 97, 145, 290, 579, and 966 ug of total linaclotide content, respectively. In all ISS analyses (tables/listings/figures), the linaclotide doses used are based on total linaclotide content unless otherwise specified. The ISS analysis database includes both the original peptide content doses for the linaclotide treatment groups as well as the adjusted linaclotide content doses for the linaclotide treatment groups for each of the 10 Phase 2/3 clinical studies.

In the phase 3 placebo-controlled trials, 852 CIC patients and 807 IBS-C patients were treated with double-blind linaclotide during the Treatment Period. In the phase 3 open-label LTS studies, 1129 CIC patients (155 RI and 974 RO) and 2146 IBS-C patients (955 RI and 1191 RO) were treated with linaclotide. Across all 10 studies, a total of 4370 patients received at least 1 dose of linaclotide. Greater than 90% of all CIC and IBS-C patients received daily doses of 145 or 290 ug linaclotide. In addition, 75 healthy volunteers also received at least 1 dose of linaclotide.

Table 44: Number of Patients Exposed to Linaclotide in the Linaclotide Clinical Program

Protocol number	Number of Patients					
	Placebo	Linaclotide, ug/d				Any dose
		< 145	145	290	> 290	
Phase 3 Placebo-Controlled Trials (Group 1)						
CIC Patients						
LIN-MD-01 (up to 12 weeks)	215	—	213	205	—	418
MCP-103-303 (up to 12 weeks)	208	—	217	217	—	434
CIC Subtotal (Treatment Period)	423		430	422		852
IBS-C Patients						
LIN-MD-31 (up to 12 weeks)	395	—	—	405	—	405
MCP-103-302 (up to 26 weeks)	403	—	—	402	—	402
IBS-C Subtotal (Treatment Period)	798			807		807
Placebo-controlled Phase 3 Total (Treatment Period)	1218	—	430	1227	—	1657
Placebo-Controlled Phase 2 Studies						
CIC Patients (Group 2)						
MCP-103-004 (up to 2 weeks)	10	12	—	10	10	32
MCP-103-201 (up to 4 weeks)	69	59	56	62	63	240
CIC Subtotal	79	71	56	72	73	272
IBS-C Patients						
MCP-103-005 (5 days)	12	12	—	—	12	24
MCP-103-202 (up to 12 weeks)	85	79	82	85	89	335
IBS-C Subtotal	97	91	82	85	101	359
Placebo-controlled Phase 2 total	176	162	138	157	174	631
Open-Label Phase 3 Studies (Group 3)						
CIC Patients						
LIN-MD-02	—	—		523	—	523
MCP-103-305	—	—		606	—	606
CIC Subtotal	—	—		1129	—	1129

Table 44 continued: Number of Patients Exposed to Linaclotide in the Linaclotide Clinical Program

Protocol number	Number of Patients					
	Placebo	Linaclotide, ug/d				
		< 145	145	290	> 290	Any dose
IBS-C Patients						
LIN-MD-02	—	—	1029	—	—	1029
MCP-103-305	—	—	1117	—	—	1117
IBS-C Subtotal	—	—	2146	—	—	2146
LTS Study Total	—	—	3270	—	—	3270
All Linaclotide Patients (Group 4)^a						
CIC Patients	—	71	1519 ^b	73	—	1627
IBS-C Patients	—	91	2609 ^c	101	—	2753
Total Number of Patients	1394	162	4128	174	—	4370

Numbers of patients may not add up due to counting of duplicate patients (see Section 4.3.4).

In Group 3, patients were required to start treatment at 290 ug but could down titrate to 145 ug for intolerable AEs. a Patients could be counted in more than one dose group in Group 4.

b Includes 1424 patients from a Phase 3 study and 95 patients from a Phase 2 study

c Includes 2493 patients from a Phase 3 study and 116 patients from a Phase 2 study

For Group 1; the mean exposure in the CIC trials was 79 days for placebo patients and 77 days for linaclotide patients; over 90% of patients were exposed to investigational product for at least 30 days. Total exposure to placebo was 92 patient-years and total exposure to linaclotide was 180 patient-years (145 ug and 290 ug doses combined). In the IBS-C trials the mean exposure to placebo was 116 days and the mean exposure to linaclotide was 112 days. Over 90% of patients were exposed to investigational product for at least 30 days, and over 40% were exposed for at least 90 days. Total exposure to placebo was 254 patient-years and total exposure to linaclotide was 247 patient-years. The longer exposure in the IBS-C trials compared to the CIC trials was a reflection of the 26-week duration of MCP-103-302. Total exposure to linaclotide across indications was 426 patient-years. See Table 45.

Table 45: Patient Exposure to Linaclotide in Phase 3 Placebo-Controlled CIC and IBS-C Trials (Group 1)—Safety Populations

Exposure	CIC Patients			IBS-C Patients		CIC + IBS-C Patients	
	Placebo (N = 423)	Linaclotide		Placebo (N = 798)	Linaclotide 290ug (N = 807)	Placebo (N = 1218)	Linaclotide (N = 1657)
		145ug (N = 430)	290ug (N = 422)				
Treatment duration, days							
Mean	79.0	77.5	76.7	116.0	111.8	103.3	93.9
SD	18.2	20.2	21.1	56.5	58.5	50.1	46.7
Median	85.0	85.0	85.0	87.0	86.0	85.0	85.0
Min, Max	5, 104	1, 102	1, 111	1, 195	1, 212	1, 195	1, 212
Treatment duration, n (%)							
≥ 1 day	423 (100)	430 (100)	422 (100)	798 (100)	807 (100)	1218 (100)	1657 (100)
≥ 7 days	421 (99.5)	424 (98.6)	412 (97.6)	791 (99.1)	792 (98.1)	1209 (99.3)	1626 (98.1)
≥ 14 days	418 (98.8)	415 (96.5)	405 (96.0)	774 (97.0)	778 (96.4)	1189 (97.6)	1596 (96.3)
≥ 30 days	398 (94.1)	400 (93.0)	392 (92.9)	735 (92.1)	731 (90.6)	1130 (92.8)	1521 (91.8)
≥ 60 days	376 (88.9)	372 (86.5)	364 (86.3)	696 (87.2)	670 (83.0)	1070 (87.8)	1404 (84.7)
≥ 90 days	25 (5.9)	20 (4.7)	14 (3.3)	357 (44.7)	335 (41.5)	382 (31.4)	368 (22.2)
≥ 120 days	0	0	0	319 (40.0)	307 (38.0)	319 (26.2)	306 (18.5)
≥ 150 days	0	0	0	309 (38.7)	299 (37.1)	309 (25.4)	298 (18.0)
≥ 180 days	0	0	0	285 (35.7)	272 (33.7)	285 (23.4)	271 (16.4)
Patient-years	91.5	91.2	88.7	253.5	247.0	344.4	426.1

Numbers of patients may not add up due to counting of duplicate patients (see Section 4.3.4).

CIC Trials: LIN-MD-01 (Treatment Period = 84 days) and MCP-103-303 (Treatment Period = 84 days); IBS-C Trials: LIN-MD-31 (Treatment Period = 84 days) and MCP-103-302 (Treatment Period = 182 days).

For Group 3; the mean exposure of CIC patients (through the cutoff date of 11-Oct-2010) was 359 days and the mean exposure of the IBS-C patients was 200 days; 79% of CIC patients and 69% of IBS-C patients were exposed to linacotide for at least 120 days. The longer mean exposure of the CIC patients occurred because the CIC Phase 3 lead-in trials were started and completed about 1 year earlier than the IBS trials, and therefore the CIC patients entered the LTS studies earlier than did the IBS-C patients; Total exposure (as of 11-Oct-2010) of CIC patients to linacotide was 1111 patient-years and total exposure of IBS-C patients to linacotide was 1177 patient-years in the LTS studies. In CIC patients, exposures to 290ug/day and 145ug/day were 893 and 218 patient-years, respectively. In IBS-C patients, exposures to 290ug/day and 145ug/day were 941 and 236 patient-years, respectively. See Table 46.

Table 46: Patient Exposure to Linacotide in the Phase 3 Open-Label Long-Term Safety Studies (Group 3)—Safety Populations

	CIC (N = 1129)	IBS-C (N = 2146)	CIC + IBS-C (N = 3270)
Treatment duration, days			
Mean	359.4	200.3	255.3
SD	190.6	129.4	170.9
Median	453.0	196.0	223.0
Min, Max	1, 570	1, 562	1, 570
Treatment duration, n (%)			
≥ 1 day	1129 (100)	2146 (100)	3270 (100)
≥ 7 days	1115 (98.8)	2101 (97.9)	3211 (98.2)
≥ 30 days	1063 (94.2)	1980 (92.3)	3038 (92.9)
≥ 60 days	975 (86.4)	1773 (82.6)	2743 (83.9)
≥ 120 days	891 (78.9)	1486 (69.2)	2373 (72.6)
≥ 180 days	853 (75.6)	1188 (55.4)	2039 (62.4)
≥ 240 days	798 (70.7)	702 (32.7)	1499 (45.8)
≥ 360 days	715 (63.3)	269 (12.5)	984 (30.1)
≥ 540 days	220 (19.5)	68 (3.2)	288 (8.8)
Patient-years	1111	1177	2285

Numbers of patients may not add up due to counting of duplicate patients
Studies: LIN-MD-02 and MCP-103-305 (cutoff date of 11-Oct-2010).
CIC = chronic constipation; IBS-C = irritable bowel syndrome with constipation

Table 47: Patient Exposure to Linacotide Across all Studies (Group 4) in the ISS—Safety Populations

	CIC Patients (N = 1627)	IBS-C Patients (N = 2753)
Treatment duration, days		
Mean	299.1	199.9
SD	236.1	13.5
Median	272.0	195.0
Min, Max	1, 667	1, 562
n	1625	2752
Treatment duration, n (%)^a		
≥ 1 day	1625 (99.9)	2752 (100)
≥ 7 days	1593 (97.9)	2667 (96.9)
≥ 30 days	1339 (82.3)	2438 (88.6)
≥ 60 days	1207 (74.2)	2181 (79.2)
≥ 120 days	975 (59.9)	1727 (62.7)
≥ 180 days	909 (55.9)	1492 (54.2)
≥ 240 days	840 (51.6)	1025 (37.2)
≥ 360 days	745 (45.8)	416 (15.1)
≥ 540 days	459 (28.2)	68 (2.5)
≥ 720 days	0	0
Patient-years	1331	1507

For Group 4; exposure is captured upon a patient's first exposure to linacotide so that data from a lead-in study for the RO patients are included in the presentation. A total of 1627 CIC and 2753 IBS-C patients were exposed to linacotide across these studies; 909 CIC and 1492 IBS-C patients were exposed for at least 6 months, and 745 CIC and 416 IBS-C patients were exposed for at least 1 year (as of the October 11, 2010 cutoff date). Total exposure of CIC patients to linacotide was 1331 patient-years and total exposure of IBS-C patients to linacotide was 1507 patient-years. See Table 47, above.

7.2.2 Explorations for Dose Response

See discussion in also Section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations – Review of Dose Ranging Trials on page 108, and Section 7.3.4 Significant Adverse Events - Dose Adjustments in the Long-Term Safety Trials on page 148.

7.2.3 Special Animal and/or In Vitro Testing

See Section 4.3 Nonclinical Nonclinical Pharmacology/Toxicology on page 27, and Section 2.5.2 Pediatric on page 16 for discussion of safety issues related to deaths in juvenile mice and contraindication and warning for use in pediatric patients.

7.2.4 Routine Clinical Testing

Medical Officer's Comments:

The clinical testing appeared to be adequate to detect most AE's. The testing for MCP-103-302 is given as an example below; the testing for the other trials was similar.

Table 48: Clinical Laboratory Tests – MCP-103-302

Clinical Chemistry:	Hematology (CBC):
Alanine transaminase (ALT)	Hematocrit
Albumin	Hemoglobin
Alkaline phosphatase	Platelet count
Aspartate aminotransferase (AST)	Red blood cell (RBC) (Erythrocyte Count)
Bicarbonate	RBC Indices
Blood urea nitrogen (BUN)	Mean corpuscular hemoglobin (MCH) Calcium
	Mean corpuscular hemoglobin concentration (MCHC)
Chloride	Mean corpuscular volume (MCV)
Cholesterol,	Absolute white blood cell (WBC) count
Creatinine	WBC differential
Glucose	
Magnesium	Complete Urinalysis:
Phosphate	Specific gravity
Potassium	pH (hydrogen ion concentration)
Sodium	Protein
Total Bilirubin	Glucose Total
Protein	Ketones Uric acid
Blood	

Urine Drug Screen: cocaine, barbiturates, amphetamines, opiates, benzodiazepine, alcohol, and cannabinoids at Screening Visit only. Clinical significance of a positive urine drug screen was assessed by the Investigator.

Pregnancy Test: serum human chorionic gonadotropin pregnancy test was conducted for all females at the Screening Visit and other visits specified in the Schedule of Evaluations. A negative urine pregnancy test for females of childbearing potential was required and had to be documented at the Randomization Visit for the patient to be eligible for randomization and dosing with study drug.

Pharmacokinetic Sample: Collected in the Triplicate ECG cohort only for determination of linaclotide and MM-419447 levels.

A complete medical history was provided by the patient at the Screening Visit. At the Screening, Week 12, and EOT Visits, each patient underwent a complete physical examination (by the investigator or a licensed health professional listed on Form FDA 1572) that included 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 assessments. Body weight was obtained at the Screening, Pretreatment, Randomization (Day 1), Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, and EOT Visits; height was measured at the Screening Visit. Vital signs, including oral temperature, systolic and diastolic blood pressure (BP), and pulse rate, were obtained in the seated position at the Screening, Pretreatment, Randomization (Day 1), Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, and EOT Visits. At the Day 1 Visit, vital signs were obtained within 30 minutes (± 5 minutes) prior to study drug administration. Pulse rate and BP readings were taken after the patient had been sitting for 5 minutes.

Electrocardiograms:

A single 12-lead ECG tracing was performed in all patients at the Screening and Week 12 and EOT Visits and documented on the appropriate eCRF. It was recommended that all patients fast for a minimum of 1 hour before clinic visits where ECGs (single or triplicate) were conducted. ECGs were electronically transmitted for analysis to the central ECG interpretation laboratory per the instructions of the laboratory and analyzed in a semiautomated fashion. ECG results were available to the investigator before the first dose of study drug was administered. Measurements were recorded for PR interval, QRS duration, RR interval, and QT interval. A T-QT study was waived in this drug.

7.2.5 Metabolic, Clearance, and Interaction Workup

There is no systemic exposure at clinically relevant doses. Linaclotide does not appear to be a substrate of CYP enzymes or an inhibitor or inducer of such enzymes. Therefore, drug-drug interaction potential is not an issue.

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

This drug is a New Molecular Entity and first in class, therefore there are no similar drugs for comparison.

7.3 Major Safety Results

7.3.1 Deaths

Medical Officer's Comments:

There were no safety signals identified in the analysis of deaths.

In total, 7 SAEs with fatal outcome were reported in the linaclotide clinical program. Six of the deaths occurred among patients who took at least one dose of linaclotide. One patient (0153115) died during the screening period prior to randomization, and did not receive any investigational product. Two patients (0090105 and 292004) died more than 30 days after the last dose of linaclotide. None of the deaths was judged to be related to treatment.

Table 49: Deaths in all Linacotide Exposed Patients

Study/ Patient No	Age, y/ Sex	Indication/ Treatment	Day of Onset o Fatal SAE ^a	Day of Death	SAE Preferred Term	Relationship
Group 1 (Phase 3 Trials)						
LIN-MD-31/ 0153115	54/M	IBS-C/ Pre Randomizatio n	NA	NA	Cardiopulmonary arrest and ventricular fibrillation ^d	NA
LIN/MD-01/ 0090105	66/F	CIC/Linacotide	(b) (6)		Pancreatic carcinoma	Unrelated
LIN-MD-01/ 0160101 ^e	49/F	CIC/Linacotide			Drug toxicity (Fentanyl)	Unlikely
Group 3 (LTS Studies)						
MCP-103-305/ 1033022 ^b	48/M	CIC/Linacotide	(b) (6)		Esophageal squamous cell cancer stage IV	Unrelated
MCP-103-305/ 0093022	68/M	CIC/Linacotide			Multiple injuries	Unrelated
MCP-103-305/ 0872010	36/F	IBS-C/ Linacotide			Drug toxicity (Morphine ^c)	Unlikely
MCP-103-305/ 292004	40/F	IBS-C/ Linacotide			Drug toxicity (Morphine and alprozolam)	Unrelated

- a Day of onset/death is in relationship to date of first dose of double-blind treatment (Day 1).
b Patient 1033022 was also enrolled under PID 0733119. The death for Patient 0733119 was reported as due to severe anemia and metastatic lung cancer (see Section 11.3.2).
c Reported as cardiac arrest in clinical study database. Changed based on updated information from Medwatch.
d Suspected drug overdose based on Emergency Room report (no autopsy)
e Patient was also enrolled as IBS-C patient 281002 in MCP-103-202
NA = not applicable (patient never received investigational product); SAE = serious adverse event.

Two of the patient deaths were due to cancer. One patient, a 48-year-old male and long-time cigarette smoker, presented with severe anemia on a study-related blood test after more than 1 year of treatment with linacotide. Further evaluation led to a diagnosis of widely metastatic esophageal cancer. The second patient, a 66-year-old female, presented with ascites 8 days after starting linacotide and was subsequently diagnosed with advanced and inoperable pancreatic cancer.

One death (a 68-year-old male) was due to multiple injuries following a fall from a ladder. The patient had a history of atrial fibrillation with rapid ventricular response, and syncopal episodes (prior to treatment with linaclotide). He was on multiple medications, some of which are associated with lightheadedness and dizziness, at the time of the fall. In addition, this patient did not report diarrhea as an AE.

Three deaths were due to drug toxicity related to the use of narcotics. All three denied drug use at trial enrollment and all three had negative initial drug screens. There was no conclusive evidence to indicate whether the 3 opioid-related deaths were unintentional fatal overdoses or intentional self-harm as no suicide notes were discovered; in these types of cases it can be difficult to determine whether a death is a suicide or the result of an unintentional fatal overdose. All 3 patients had IBS-C and psychiatric comorbidities (bipolar disorder, anxiety, situational depression); 2 of the 3 had a known history of substance abuse. Drugs may also have played a role in an additional death that occurred prior to randomization; this patient died due to cardiopulmonary arrest and ventricular fibrillation, which were suspected to be related to substance overdose (unspecified). Patients with IBS or a history of substance abuse are at a higher risk for suicidal behavior than the general population

7.3.2 Nonfatal Serious Adverse Events

Medical Officer's Comment:

For the controlled phase 3 trials, 19 (1.6%) placebo patients and 23 (1.4%) linaclotide patients experienced at least 1 on-therapy SAE during the Treatment Period. There was no clinically meaningful difference between linaclotide and placebo patients in the proportion of patients reporting SAEs based on SOC. There was no meaningful difference in the SAE incidence between the 2 linaclotide doses. There were no SAEs of diarrhea. No specific SAE was reported in more than 1 linaclotide patient during the Treatment Period

For the long-term safety trials the applicant reported no SAE's of diarrhea. However there was one patient in the long-term trials, a 24 yo female with CIC who had an SAE of dehydration and orthostatic hypotension who also had diarrhea, nausea and vomiting. The episode was reported as drug related by the Investigator, though it may have been secondary to biliary dyskinesia.

Group 1 – Pooled CIC Patients – Phase 3 Controlled Trials

A total of 10 (2.4%) placebo patients and 17 (2.0%) linaclotide patients experienced at least 1 SAE. There was no meaningful difference in the SAE incidence between the 2 linaclotide doses. Although there were no SAEs of diarrhea, diarrhea was reported in one patient as an AE along with the SAEs of dehydration and orthostatic hypotension. No specific SAE was reported in more than 1 linaclotide patient; atrial fibrillation was reported by 2 placebo patients. See Table 50.

Table 50: Incidence of On-Therapy Serious Adverse Events in CIC Patients in the Phase 3 Placebo-Controlled Trials (Group 1) —Safety Population

System Organ Class Preferred Term	Number (%) of Patients			
	Placebo (N = 423)	Linaclotid		
		145 ug/day (N = 430)	290 ug/day (N = 422)	Linaclotide Total (N = 852)
Any SAE	10 (2.4)	6 (1.4)	11 (2.6)	17 (2.0)
CARDIAC DISORDERS	3 (0.7)	1 (0.2)	0	1 (0.1)
Atrial Fibrillation ^a	2 (0.5)	1 (0.2)	0	1 (0.1)
Angina pectoris	1 (0.2)	0	0	0
ENDOCRINE DISORDERS	1 (0.2)	0	0	0
Goiter	1 (0.2)	0	0	0
GASTROINTESTINAL DISORDERS	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.2)
Diverticulum intestinal hemorrhagic	0	0	1 (0.2)	1 (0.1)
Intestinal obstruction	0	1 (0.2)	0	1 (0.1)
Inguinal hernia	1 (0.2)	0	0	0
GENERAL DISORDERS/ ADMINISTRATION SITE CONDITIONS	0	1 (0.2)	0	1 (0.1)
Chest pain	0	1 (0.2)	0	1 (0.1)
HEPATOBIILIARY DISORDERS	1 (0.2)	0	1 (0.2)	1 (0.1)
Cholecystitis	0	0	1 (0.2)	1 (0.1)
Cholelithiasis	1 (0.2)	0	0	0
INFECTIONS AND INFESTATIONS	4 (0.9)	2 (0.5)	3 (0.7)	5 (0.6)
Bronchitis	1 (0.2)	1 (0.2)	0	1 (0.1)
Cellulitis	1 (0.2)	0	1 (0.2)	1 (0.1)
Diverticulitis	0	0	1 (0.2)	1 (0.1)
Pneumonia	1 (0.2)	1 (0.2)	0	1 (0.1)
Postoperative wound infection	0	0	1 (0.2)	1 (0.1)
Gastroenteritis viral	1 (0.2)	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (0.2)	0	1 (0.1)
Drug toxicity	0	1 (0.2)	0	1 (0.1)

System Organ Class Preferred Term	Number (%) of Patients			
	Placebo (N = 423)	Linaclotid		
		145 ug/day (N = 430)	290 ug/day (N = 422)	Linaclotide Total (N = 852)
METABOLISM AND NUTRITION DISORDERS	0	0	1 (0.2)	1 (0.1)
Dehydration	0	0	1 (0.2)	1 (0.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED	1 (0.2)	0	2 (0.5)	2 (0.2)
Lymphoma	0	0	1 (0.2)	1 (0.1)
Pancreatic carcinoma	0	0	1 (0.2)	1 (0.1)
Parathyroid tumor benign	1 (0.2)	0	0	0
NERVOUS SYSTEM DISORDERS	0	0	1 (0.2)	1 (0.1)
Cerebrovascular disorder	0	0	1 (0.2)	1 (0.1)
PREGNANCY, PUERPERIUM AND PERINATAL CONDISTIONS	0	0	1 (0.2)	1 (0.1)
Ectopic pregnancy	0	0	1 (0.2)	1 (0.1)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	1 (0.2)	1 (0.1)
Endometriosis	0	0	1 (0.2)	1 (0.1)
VASCULAR DISORDERS	0	0	1 (0.2)	1 (0.1)
Orthostatic hypotension	0	0	1 (0.2)	1 (0.1)

TEAE = treatment-emergent adverse event.

a An additional SAE of atrial fibrillation occurred in a patient on 145 ug linaclotide during the Randomized Withdrawal Period.

Group 1 – Pooled IBS-C Patients – Phase 3 Controlled Trials

A total of 9 (1.1%) placebo patients and 6 (0.7%) linaclotide patients experienced at least 1 SAE. No specific SAE was reported in more than one linaclotide patient. There were no SAEs of diarrhea. See Table 51.

In addition to the SAEs listed in the above table, there was one linaclotide IBS-C patient who had an SAE of biliary dyskinesia that occurred during the LTS extension study, but within 30 days of the last dose of linaclotide during the Treatment Period of the lead-in study. Of the 7 SAEs that were reported in the linaclotide patients, 2 (pericarditis and pericardial perfusion in 1 patient) were judged by the Investigator to be possibly related to treatment.

Table 51: Incidence of On-Therapy Serious Adverse Events in IBS-C Patients in the Phase 3 Placebo-Controlled Trials (Group 1) —Safety Population

System Organ Class Preferred Term	Number (%) of Patients	
	Placebo (N =798)	Linacotide 290 ug/day (N = 807)
Any SAE	9 (1.1)	6 (0.7)
CARDIAC DISORDERS	0	1 (0.1)
Pericardial effusion	0	1 (0.1)
Pericarditis	0	1 (0.1)
EAR AND LABYRINTH DISORDERS	1 (0.1)	0
Vertigo	1 (0.1)	0
GASTROINTESTINAL DISORDERS	2 (0.3)	0
Abdominal pain lower	1 (0.1)	0
Duodenitis	1 (0.1)	0
Hiatus hernia	1 (0.1)	0
Esophagitis	1 (0.1)	0
HEPATOBIILIARY DISORDERS	1 (0.1)	0
Cholecystitis chronic	1 (0.1)	0
INFECTIONS AND INFESTATIONS	2 (0.3)	1 (0.1)
Appendicitis	0	1 (0.1)
Bronchitis	1 (0.1)	0
Gastroenteritis	1 (0.1)	0
Pneumonia viral	1 (01)	0
Urinary tract infection	1 (0.1)	0

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (0.1)
Rotator cuff syndrome	0	1 (0.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED	2 (0.3)	1 (0.1)
Hodgkin's disease nodular sclerosis stage IV	0	1 (0.1)
Rectal cancer stage IV	1 (0.1)	0
Uterine leiomyoma	1 (0.1)	0
NERVOUS SYSTEM DISORDERS	1 (0.1)	0
Transient ischemic attack	1 (0.1)	0
RENAL AND URINARY DISORDERS	1 (0.1)	0
Renal cyst	1 (0.1)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	1 (0.1)
Asthma	0	1 (0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.1)	0
Angioedema	1 (0.1)	0
SURGICAL AND MEDICAL PROCEDURES	0	1 (0.1)
Cystopexy	0	1 (0.1)

Group 1 – Pooled CIC and IBS-C Patients

In total, 19 (1.6%) placebo patients and 23 (1.4%) linaclotide patients experienced at least 1 on-therapy SAE during the Treatment Period. There was no clinically meaningful difference between linaclotide and placebo patients in the proportion of patients reporting SAEs based on SOC. There was no meaningful difference in the SAE incidence between the 2 linaclotide doses. There were no SAEs of diarrhea. No specific SAE was reported in more than 1 linaclotide patient during the Treatment Period.

Group 2 – Phase 2 Controlled Trials

No SAEs were reported among the 272 CIC patients who were treated with linaclotide in the phase 2 placebo-controlled studies (Group 2) One SAE (fecaloma) was reported

among the 335 IBS-C patients who were treated with linaclotide in the phase 2 placebo-controlled study. The patient was hospitalized for treatment and the fecaloma resolved 1 day after onset; the patient resumed treatment (290 ug/day) with no other TEAEs reported.

Group 3 - Phase 3 Open-Label Long-Term Safety Studies

In total, 129 (3.9%) of 3270 patients experienced at least 1 SAE. SAEs that were reported in 3 or more patients were cholelithiasis (7 patients); chest pain and breast cancer (5 patients each); back pain, osteoarthritis, fall, and syncope (4 patients each); and biliary dyskinesia, bronchitis, cystocele, diverticulitis, gastroesophageal reflux disease, non-cardiac chest pain, and uterine prolapse (3 patients each). There were 2 cases of gastroenteritis, one a confirmed case of salmonella, and the other with predominant upper GI symptoms with no diarrhea. There was one patient who had an SAE of aplastic anemia which appeared to be spontaneous and not drug related.

GI SAEs

Since linaclotide has low systemic exposure and exerts its pharmacologic effect with the lumen of the GI tract, SAEs of the GI SOC are of special interest. See Table 52 below and also see discussion of Gastrointestinal AE's in Section 7.3.5 Submission Specific Primary Safety Concerns on page 150.

Table 52: Linaclotide-Treated Patients Who Had SAEs in the Gastrointestinal Disorders SOC

Preferred Term	Double-blind N = 2790	LTS (N = 3270)
	Patient PID	
Gastroesophageal reflux disease		0430103 0033008 1013007
Abdominal pain		0310135 0703115
Diverticular perforation		0093006 0403008
Intestinal obstruction	0690108	0083114
Nausea		0413120 0613108
Pancreatitis		0310135 0632035
Vomiting		0413120 0613108
Abdominal Pain Upper		0413120
Diverticulum intestinal hemorrhagic	1033017	
Fecaloma	23109	
Gastric ulcer perforation		057020 ^b
Hemorrhoids		0243010
Ileus		260001
Malocclusion		1003001
Peritonitis		0403008
Rectal prolapse		0950143
Small intestinal obstruction		0293106
Spigelian hernia		0330101

a Phase 2b SAE

b MCP-103-305 PID = 0095006

7.3.3 Dropouts and/or Discontinuations

Medical Officer's Comment:

There was a higher incidence of discontinuations in the treatment arm (8.5%) than in the placebo arm (3.4%) in the controlled trials. The majority of these were secondary to diarrhea (4.8%), however there was no significant difference in incidence of diarrhea or GI AE's between the two doses in the CIC trials. In the long term safety trials AE's resulting in discontinuations occurred in 10.2% of patients, with 4.9% secondary to diarrhea. Discontinuations were similar between indications and doses.

More than one AE was allowed to be reported as a reason for a patient to discontinue from a study. Therefore, multiple AEs may be associated with an individual patient's

withdrawal. Conversely, some AEs may have been reported at the time of a patient's withdrawal but were not reported as a cause for discontinuation and therefore do not appear as ADOs.

Group 1 – Pooled CIC patients

Eighteen (4.3%) placebo patients and 65 (7.6%) linaclotide patients discontinued from the study because of an AE. The AEs that resulted in the discontinuation of $\geq 1\%$ of linaclotide patients were diarrhea (4.2%) and abdominal pain (1.1%). Five (5) of the 9 linaclotide patients who withdrew from the trial because of abdominal pain also reported concomitant diarrhea as a reason for discontinuation and 1 patient (0240109) reported diarrhea as an AE at the time of discontinuation. Of the 3 placebo patients who withdrew because of abdominal pain, 2 reported concomitant diarrhea as an AE. There was no difference in the discontinuation rate between the 2 linaclotide doses. See Table 53.

Table 53: Adverse Events Resulting in Discontinuation of at Least 2 Linacotide CIC Patients from the Phase 3 Placebo-Controlled Trials (Group 1)—Safety Population

Preferred Term	Number (%) of Patients			
	Placebo (N = 423)	Linacotide		
		145 ug/day (N = 430)	290 ug/day (N = 422)	Linacotide Total (N = 852)
Patients with ADOs	18 (4.3)	34 (7.9)	31 (7.3)	65 (7.6)
Diarrhea	2 (0.5)	20 (4.7)	16 (3.8)	36 (4.2)
Abdominal pain	3 (0.7)	5 (1.2)	4 (0.9)	9 (1.1)
Nausea	2 (0.5)	3 (0.7)	1 (0.2)	4 (0.5)
Abdominal distension	0	3 (0.7)	0	3 (0.4)
Abdominal pain upper	0	3 (0.7)	0	3 (0.4)
Defecation urgency	0	1 (0.2)	2 (0.5)	3 (0.4)
Fecal incontinence	0	2 (0.5)	1 (0.2)	3 (0.4)
Dehydration	0	0	2 (0.5)	2 (0.2)
Dyspepsia	0	2 (0.5)	0	2 (0.2)
Flatulence	1 (0.2)	2 (0.5)	0	2 (0.2)
Headache	3 (0.7)	1 (0.2)	1 (0.2)	2 (0.2)

ADO = adverse event leading to dropout.

Group 1 – Polled IBS-C Patients

Twenty-three (2.9%) placebo patients and 76 (9.4%) linacotide patients discontinued from the study because of an AE. The AEs that resulted in the discontinuation of $\geq 1\%$ of linacotide patients were diarrhea (5.3%) and abdominal pain (1.2%). Seven (7) of the 10 patients who withdrew from the trial because of abdominal pain also reported concomitant diarrhea as a reason for discontinuation and the other 3 (0602017, 1092031, and 1142005) reported diarrhea as an AE at the time of discontinuation. Two patients discontinued due to rash, neither of which was reported to be urticarial. See Table 54.

Table 54: Adverse Events Resulting in Discontinuation of at Least 2 Linacotide IBS-C Patients from the Phase 3 Placebo-Controlled Trials—Safety Population

Preferred Term	Number (%) of Patients	
	Placebo (N = 798)	Linacotide 290 ug/day (N = 807)
Patients with ADOs	23 (2.9)	76 (9.4)
Diarrhea	3 (0.4)	43 (5.3)
Abdominal pain	0	10 (1.2)
Abdominal distension	2 (0.3)	3 (0.4)
Flatulence	0	3 (0.4)
Nausea	1 (0.1)	3 (0.4)
Defecation urgency	0	2 (0.2)
Headache	1 (0.1)	2 (0.2)
Rash	0	2 (0.2)

ADO = adverse event leading to dropout.

Group 1 – Pooled CIC and IBS-C Patients

As was presented for each indication separately, the AEs that resulted in the discontinuation of $\geq 1\%$ of linaclotide patients were diarrhea (4.8% of linaclotide patients' vs. 0.4% of placebo patients) and abdominal pain (1.1% of linaclotide patients vs. 0.2% of placebo patients). The incidence of ADOs did not differ between the 2 doses. See Table 55.

Table 55: Adverse Events Resulting in Discontinuation of at Least 2 Linaclotide Patients From the Phase 3 Placebo-Controlled Trials Overall (Group 1)—Safety Population

Preferred Term	Number (%) of Patients			
	Placebo (N = 1218)	Linaclotide		
		145 ug/day (N = 430)	290 ug/day (N = 1227)	Linaclotide Total (N = 1657)
Patients with ADOs ^a	41 (3.4)	34 (7.9)	107 (8.7)	141 (8.5)
Diarrhea	5 (0.4)	20 (4.7)	59 (4.8)	79 (4.8)
Abdominal pain	3 (0.2)	5 (1.2)	14 (1.1)	19 (1.1)
Nausea	3 (0.2)	3 (0.7)	4 (0.3)	7 (0.4)
Abdominal distension	2 (0.2)	3 (0.7)	3 (0.2)	6 (0.4)
Defecation urgency	0	1 (0.2)	4 (0.3)	5 (0.3)
Flatulence	1 (0.1)	2 (0.5)	3 (0.2)	5 (0.3)
Fecal incontinence	0	2 (0.5)	2 (0.2)	4 (0.2)
Headache	4 (0.3)	1 (0.2)	3 (0.2)	4 (0.2)
Abdominal pain upper	0	3 (0.7)	0	3 (0.2)
Dyspepsia	0	2 (0.5)	1 (0.1)	3 (0.2)
Dehydration	0	0	2 (0.2)	2 (0.1)
Rash	0	0	2 (0.2)	2 (0.1)
Vomiting	1 (0.1)	1 (0.2)	1 (0.1)	2 (0.1)

^a Includes all AEs leading to discontinuation, regardless of whether the event was treatment-related.
 ADO = adverse event leading to dropout

Ongoing Adverse Events at Time of Withdrawal (non-ADOs)

In the Phase 3 placebo-controlled trials, more linaclotide than placebo patients (i.e., > 1%) discontinued due to withdrawal of consent (CIC patients) or lost to follow up (CIC and IBS-C). In this section, the AEs that were ongoing at the time of discontinuation are examined to determine if there might be an underlying safety reason for this difference. In order to assess the potential for AEs to have contributed to patient discontinuations, patients who withdrew consent were interviewed at the time of withdrawal, and attempts were made to contact patients who were lost to follow-up.

Overall, there were 85 linaclotide and 60 placebo patients who withdrew consent; of these patients, ongoing AEs were reported in 8 (9.4%) linaclotide and 5 (8.3%) placebo patients. The only AE reported in more than one linaclotide patient was fatigue (2 patients). The AEs reported by more than one placebo patient were depression and urinary tract infection (2 patients each).

Overall, there were 64 linaclotide and 27 placebo patients who were lost to follow-up (After-text Table 4.1.3.6A); of these patients, ongoing TEAEs were reported in 12 (18.8%) linaclotide and 7 (25.9%) placebo patients. Diarrhea was the most common ongoing TEAE, reported in 3 (4.7%) linaclotide patients (and no placebo patients). The other TEAEs reported in more than one linaclotide patient were headache (3 patients), and abdominal pain and flatulence (2 patients each). No specific TEAE (preferred term) was reported in more than one placebo patient.

Group 2 – Phase 2 and IBS-C Trials

The incidence of AEs that led to discontinuation of the CIC patients from the Phase 2 double-blind placebo-controlled studies (Group 2) are In total, 2 (2.5%) placebo patients and 7 (2.6%) linaclotide patients discontinued from the studies because of an AE. In the placebo group, the reasons for discontinuation were abdominal pain, flatulence, and painful defecation (1 patient) and food poisoning (1 patient). In the linaclotide group, 6 patients discontinued because of diarrhea (one case of which was also associated with abdominal pain and abnormal gastrointestinal sounds) and 1 patient discontinued because of a balance disorder. The patients who discontinued due to diarrhea were treated with linaclotide doses of 145 ug/day (1 [1.8%] patient), 290 ug/day (2 [2.8%] patients), and 579 ug/day (3 [4.8%] patients).

In the IBS-C studies, there were 2 (2.4%) placebo patients and 23 (6.9%) linaclotide patients who discontinued as a result of AEs (all in MCP-103-202). In the placebo group, the reasons for discontinuation were abdominal distension and flatulence (1 patient) and hepatic enzymes increased (1 patient). Of the 23 linaclotide patients, 13 discontinued due to diarrhea (either alone or in combination with abdominal pain). The patients who discontinued due to diarrhea had received linaclotide doses of 72 ug/day (2 [2.5%] patients), 145 ug/day (4 [4.9%] patients), 290 ug/day (1 [1.2%] patients), and 579 ug/day (6 [6.7%] patients).

Group 3 - Phase 3 Open-Label Long-Term Safety Studies

The percentages of patients who had ADOs was similar across indications; diarrhea was the most frequently reported ADO (4.9% overall).

Table 56: Adverse Events Resulting in Discontinuation of at Least 3 Patients in the Phase 3 Open-Label Long-Term Safety Studies (Group 3) —Safety Population

Adverse Event (Preferred Term)	Number (%) of Patients		
	Total CIC (N = 1129)	Total IBS-C (N = 2146)	Total CIC + IBS-C (N = 3270)
Patient with ADOs ^a	123 (10.9)	211 (9.8)	333 (10.2)
Diarrhea	54 (4.8)	106 (4.9)	160 (4.9)
Abdominal pain	6 (0.5)	20 (0.9)	26 (0.8)
Abdominal distension	7 (0.6)	7 (0.3)	14 (0.4)
Flatulence	6 (0.5)	8 (0.4)	14 (0.4)
Nausea	7 (0.6)	5 (0.2)	12 (0.4)
Abdominal pain upper	4 (0.4)	3 (0.1)	7 (0.2)
Constipation	3 (0.3)	4 (0.2)	7 (0.2)
Abdominal pain lower	1 (0.1)	4 (0.2)	5 (0.2)
Defecation urgency	0	5 (0.2)	5 (0.2)
Hypertension	3 (0.3)	2 (0.1)	5 (0.2)
Abdominal discomfort	2 (0.2)	2 (0.1)	4 (0.1)
Anemia	0	5 (0.2) ^a	4 (0.1)
Breast cancer	1 (0.1)	3 (0.1)	4 (0.1)
Fecal incontinence	1 (0.1)	3 (0.1)	4 (0.1)
Gastroesophageal reflux disease	3 (0.3)	1 (0.0)	4 (0.1)
Diverticulitis	2 (0.2)	1 (0.0)	3 (0.1)
Dizziness	0	3 (0.1)	3 (0.1)
Hepatic enzyme increased	2 (0.2)	1 (0.0)	3 (0.1)
Palpitations	2 (0.2)	1 (0.0)	3 (0.1)
Vomiting	1 (0.1)	2 (0.1)	3 (0.1)

Numbers of patients may not add up due to counting of duplicate patients (see Section 4.3.4).

^a Included a duplicate patient

TEAEs are ordered by decreasing frequency among all patients

Group 4S – Phase 3 Double-Blind and/or Open-Label Trials

The percentage of patients who had ADOs was lower in the phase 3 RO patients than in the RI patients and the P3 other patients. This difference was most evident for the ADO of diarrhea, which was 3.0% among the Phase 3 linaclotide RO patients versus 8.4% in the RI patients and 8.8% in P3 Other patients.

Table 57: Adverse Events Resulting in Discontinuation of at Least 3 CIC or IBS-C Patients in the Phase 3 Placebo-Controlled or Open-Label Long-Term Safety Studies (Group 4S)—Safety Population

Adverse Event (Preferred Term)	P3 LIN RO	P3 Other	P3 Total	P2 RO	RI	Total
	N = 1522	N = 1076	N = 2598	N = 205	N = 1108	N = 3910
n (%)						
Patient with ADOs ^a	120 (7.9)	166 (15.4)	286 (11.0)	25 (12.2)	167 (15.1)	478 (12.2)
Diarrhea	46 (3.0)	95 (8.8)	141 (5.4)	8 (3.9)	93 (8.4)	242 (6.2)
Abdominal pain	11 (0.7)	21 (2.0)	32 (1.2)	2 (1.0)	12 (1.1)	46 (1.2)
Abdominal distension	5 (0.3)	5 (0.5)	10 (0.4)	2 (1.0)	8 (0.7)	20 (0.5)
Flatulence	1 (0.1)	8 (0.7)	9 (0.3)	2 (1.0)	8 (0.7)	19 (0.5)
Nausea	4 (0.3)	7 (0.7)	11 (0.4)	1 (0.5)	7 (0.6)	19 (0.5)
Abdominal pain upper	2 (0.1)	4 (0.4)	6 (0.2)	1 (0.5)	3 (0.3)	10 (0.3)
Defecation urgency	1 (0.1)	5 (0.5)	6 (0.2)	1 (0.5)	3 (0.3)	10 (0.3)
Fecal incontinence	0	5 (0.5)	5 (0.2)	0	3 (0.3)	8 (0.2)
Constipation	3 (0.2)	0	3 (0.1)	2 (1.0)	2 (0.2)	7 (0.2)
Abdominal discomfort	2 (0.1)	3 (0.3)	5 (0.2)	0	1 (0.1)	6 (0.2)
Abdominal pain lower	2 (0.1)	2 (0.2)	4 (0.2)	0	2 (0.2)	6 (0.2)
Dyspepsia	1 (0.1)	3 (0.3)	4 (0.2)	0	1 (0.1)	5 (0.1)
Gastroesophageal reflux disease	2 (0.1)	2 (0.2)	4 (0.2)	0	1 (0.1)	5 (0.1)
Headache	1 (0.1)	4 (0.4)	5 (0.2)	0	0	5 (0.1)
Hypertension	2 (0.1)	1 (0.1)	3 (0.1)	0	2 (0.2)	5 (0.1)
Vomiting	2 (0.1)	2 (0.2)	4 (0.2)	0	1 (0.1)	5 (0.1)
Anemia	1 (0.1)	0	1 (0.0)	0	3 (0.3)	4 (0.1)
Breast cancer	1 (0.1)	0	1 (0.0)	1 (0.5)	2 (0.2)	4 (0.1)
Dizziness	1 (0.1)	1 (0.1)	2 (0.1)	0	2 (0.2)	4 (0.1)

Continued next page

Table 57 continued

Adverse Event (Preferred Term)	P3 LIN RO	P3 Other	P3 Total	P2 RO	RI	Total
	N = 1522	N = 1076	N = 2598	N = 205	N = 1108	N = 3910
n (%)						
Hepatic enzyme	1 (0.1)	2 (0.2)	3 (0.1)	0	1 (0.1)	4 (0.1)
Diverticulitis	2 (0.1)	0	2 (0.1)	0	1 (0.1)	3 (0.1)
Frequent bowel	0	1 (0.1)	1 (0.0)	0	2 (0.2)	3 (0.1)
Hemorrhoids	1 (0.1)	1 (0.1)	2 (0.1)	1 (0.5)	0	3 (0.1)
Palpitations	2 (0.1)	0	2 (0.1)	0	1 (0.1)	3 (0.1)
Urinary tract infection	2 (0.1)	1 (0.1)	3 (0.1)	0	0	3 (0.1)
White blood cell count decreased	2 (0.1)	1 (0.1)	3 (0.1)	0	0	3 (0.1)

P2 = phase 2; P3 = phase 3; LIN = linaclotide; RI = randomization ineligible; RO = rollover;

P3 LIN RO = Patients who received linaclotide in both a Phase 3 DB study (either during the Treatment Period or the RW Period) and an open-label long-term safety study.

P3 Others = Patients who received only placebo in a Phase 3 DB study followed by Linaclotide treatment in an LTSS or received linaclotide in a Phase 3 DB study only without enrolling in an LTSS.

P3 Total = P3 LIN RO + P3 Others;

P2 RO = Patients who completed a Phase 2 study and then rolled over into an LTSS.

RI = Patients who failed to be randomization eligible in a Phase 3 DB study and then enrolled in an LTSS.

Total = P3 Total + P2 RO + RI, in which a patient who enrolled in more than 1 Group 4 study was counted once

There were no ADOs in the Phase 1 studies.

7.3.4 Significant Adverse Events

Medical Officer's Comments:

Dose reduction from 290ug to 145ug was performed in 32% of the patients in the long-term safety trials, approximately half of these patients then completed the trial and half required discontinuation of linaclotide. The far majority of the patients required dose suspension or reduction for the AE of diarrhea, this most commonly occurred in the first 3 weeks of the trial. Analysis of the group of patients who received dose reductions showed no evidence of significant differences in demographic or baseline characteristics compared to the general population in the trials.

See discussion in Section 7.3.5 Submission Specific Primary Safety Concerns on page 150 and Section 7.4.1 Common Adverse Events on page 168.

Dose Adjustments in the Long-Term Safety Trials

All patients in the LTS studies received 290ug linaclotide initially. Patients, who experienced AEs intolerable enough to prompt consideration of study withdrawal could, at the discretion of the investigator, have either of the following two interventions: (1) a temporary suspension of dosing, or (2) a reduction in their dose of linaclotide (from 290ug to 145ug). After a temporary suspension in dosing, patients could resume either the 145ug or 290ug of linaclotide at the discretion of the Investigator. Once a patient's dose had been decreased, subsequent dose adjustments (increases or decreases between 290ug and 145ug) were permitted, also at the discretion of the Investigator.

Table 58 and

Table 59 present the number of patients who did and did not have dose adjustments during the LTS studies. As of the 11-Jun-2011 cutoff date, 2225 (68%) of the 3271 Group 3 patients had taken the 290 ug dose without having had a dose reduction or temporary dose suspension compared with 1046 (32%) patients who had a dose reduction or suspension: 773 [715+58] patients (24%) remained on the 145 ug dose throughout their subsequent participation in the LTS studies, while 177 [93+47+37] (5%) resumed the 290 ug dose by the time of the last observation.

Table 58: Dose Adjustment Patterns for Patients in the Open-label Long-term Safety Studies (Group 3)—Safety Population

Dose Adjustment Pattern (from first dose to last dose observed)	CIC (N = 1129)	IBS-C (N = 2146)	CIC + IBS-C (N = 3270)
	n (%)	n (%)	n (%)
290 ug only	784 (69)	1497 (70)	2277 (70)
290 ug - 145 ug	237 (21)	464 (22)	701 (21)
290 ug - 145 ug - 290 ug	29 (3)	45 (2)	74 (2)
290 ug - suspension - 145 ug	9 (1)	44 (2)	53 (2)
290 ug - suspension - 290 ug	21 (2)	27 (1)	48 (1)
Other, 145 ug at last observation	31 (3)	41 (2)	72 (2)
Other, 290 ug at last observation	15 (1)	18 (1)	33 (1)
Other, suspension at last observation	3 (< 1)	10 (< 1)	12 (< 1)

Numbers of patients may not add up due to counting of duplicate patients (From 120-day safety update).

Table 59: Summary of Patients who had Dose Adjustments in Open-Label Long-Term Safety Trials (Group 3)

	CIC (N = 1129)	IBS-C (N = 2147)	CIC + IBS-C (N = 3271)
	n (%)	n (%)	n (%)
No dose adjustment (290 ug dose maintained)	783 (69)	1446 (67)	2225 (68)
Patient ongoing or completed study	425 (38)	854 (40)	1279 (39)
Patient discontinued early	358 (32)	592 (28)	946 (29)
Due to GI SOC AE	34 (3)	45 (2)	79 (2)
Due to Non-GI SOC AE	27 (2)	44 (2)	71 (2)
Due to reasons not related to AEs	297 (26)	503 (23)	796 (24)
Dose adjustment (Received low dose and/or dose suspension)	346 (31)	701 (33)	1046 (32)
Patient ongoing or completed study	173 (15)	352 (16)	525 (16)
Patient discontinued early	173 (15)	349 (16)	521 (16)
Due to GI SOC AE	57 (5)	142 (7)	199 (6)
Due to Non-GI SOC AE	11 (1)	19 (1)	29 (1)
Due to reasons not related to AEs	105 (9)	188 (9)	293 (9)

Numbers of patients may not add up due to counting of duplicate patients.
From 120-day safety update

Table 60: Dose adjustments patterns in Long-term Safety Group

Time to First Dose Adjustment	CIC	IBS-C	CIC +
	n (%)	(N = n (%))	IBS-C (N n (%))
Patients with dose adjustment	346 (31)	701 (33)	1046 (32)
Week 1	32 (3)	72 (3)	104 (3)
Weeks 2-4	138 (12)	282 (13)	420 (13)
Weeks 5-8	67 (6)	158 (7)	225 (7)
Weeks 9-12	15 (1)	21 (1)	36 (1)
Weeks 13-24	49 (4)	74 (3)	122 (4)
Weeks 25-48	29 (3)	73 (3)	102 (3)
Week 49 and beyond	16 (1)	21 (1)	37 (1)

Numbers of patients may not add up due to counting of duplicate patients.
From 120-day safety update

Table 61: Adverse Events Resulting in Dose Adjustment in the Long Term Safety Trials

Adverse Event Resulting in Dose Adjustment	Number (%) of Patients		
	CIC N = 1129	IBS-C N = 2147	CIC + IBS-C N = 3271
Any TEAE	317 (28.1)	618 (28.8)	934 (28.6) ^b
GI SOC ^a	289 (25.6)	560 (26.1)	849 (26.0)
Diarrhea	253 (22.4)	487 (22.7)	740 (22.6)
Abdominal pain	22 (1.9)	35 (1.6)	57 (1.7)
Defecation urgency	10 (0.9)	26 (1.2)	36 (1.1)
Flatulence	11 (1.0)	14 (0.7)	25 (0.8)

Numbers of patients may not add up due to counting of duplicate patients.

A Patients may have been counted under more than 1 GI TEAE.

B An additional 116 patients who had dose adjustments did not have a corresponding TEAE reported as of the cutoff date of 11-Jun-2011 and are not captured in this table.

7.3.5 Submission Specific Primary Safety Concerns

For discussion of Immunogenicity See discussion in Section 7.4.6 Immunogenicity on page 188.

Gastrointestinal Severe Adverse Events

Since linaclotide has low systemic exposure and exerts its pharmacologic effect with the lumen of the GI tract, SAEs of the GI SOC are of special interest.

The SAEs in the GI SOC include 3 cases of bowel obstruction: Patient 0690108 due to an internal hernia related to intestinal adhesions from previous surgery; Patient 0083114 due to cecal volvulus; and Patient 0293106 due to small intestinal obstruction, a subacute mechanical obstruction in a patient who had previous pelvic surgery. The first two patients withdrew from treatment with linaclotide but the third patient was able to continue linaclotide treatment. Besides the 3 cases of obstruction there was one case of ileus (Patient 260001) in a patient with recent abdominal and pelvic surgery who withdrew from treatment with linaclotide.

There were 2 cases of diverticular perforation (Patients 0403008 and 0093006), one case of diverticular hemorrhage (Patient 1033017), and 4 cases of diverticulitis (Patients 0362079, 1013017, 0450108, and 0290103). All patients except Patients 0093006 and 0290103 had a history of diverticulosis. Diverticulitis is a TEAE reported under the Infections and Infestations SOC.

Three SAEs of gastrointestinal reflux disease were reported (Patients 0430103, 0033008, and 1013007), two of those were exacerbations of pre-existing conditions.

Two cases of pancreatitis were reported (Patients 0632035 and 0310135), both secondary to gallstones.

One abdominal pain SAE was reported in isolation (Patient 0703115) and 2 abdominal pain SAEs were reported in association with other SAEs (Patient 0310135, abdominal pain with cholelithiasis and pancreatitis, and Patient 0413120, abdominal pain upper with nausea and vomiting). Two SAEs of nausea and vomiting were reported together in association with other clinical events (Patient 0613108 with bladder adhesions, and Patient 0413120 noted above). The other GI SAEs were individual occurrences.

Patient 0413120 was 24yo female with CIC who was admitted to the hospital for hydration and antibiotics secondary to upper abdominal pain, diarrhea and nausea and vomiting. This was thought to be drug related by the investigator, however it may have been secondary to biliary colic with a positive nuclear scan.

Ischemic Colitis

Medical Officer's Comments:

The applicant initially did not report any cases of ischemic colitis (IC) and initially did not analyze for this AE. However, the agency identified one safety report for a case of ischemic colitis reported after last date of data collection for the final reports and the 120-day safety update from the open-label long term safety trials. Another case was also first noted in a safety report, but did appear in the 120 day safety update; however it was not identified by the applicant. One more case was noted in the phase 2 CIC trials. Extensive review of the data was undertaken both by the applicant and the Division; no other probable cases were identified. Analysis of the possibility of IC being

related to linaclotide is presented below along with the narratives for each of the three cases identified.

Note, all three cases occurred in patients with risk factors for ischemic colitis, the one in the phase 2 trials was 10 days after the patient took only 13 days of linaclotide. The two in the phase 3 long term trials were after the patients had received drug for over one year. It is the investigators and this reviewer's opinion that these are unlikely to be drug related. No cases were noted in the shorter controlled phase 3 trials including the placebo group. I agree with the applicants' conclusion that these cases are consistent with the incidence rate IC seen in other large population-based cohort studies. This reviewer does not think there is a safety signal present, however Post-marketing Surveillance and Reporting of any cases of ischemic colitis should be performed. In addition, wording to prompt physicians and patients to stop linaclotide and seek medical evaluation for any severe abdominal pain and/or bloody diarrhea should be included in the labeling, so that patients will not ignore symptoms of other possibly serious conditions.

The Applicants Analysis and Rational for the Possibility of Ischemic Colitis being Drug Related

Fourteen patients met the criteria for Cases of Interest and were subjected to further adjudication:

- 3 patients were previously identified as having IC by the investigators during the clinical studies
- 4 patients were identified by FDA as having Important GI Events requiring additional investigation
- 7 patients met the clinical criteria for Case of Interest by having abdominal pain within 72 hours of reporting lower GI bleeding

The data from the 14 Cases of Interest were evaluated by the Expert Panel the applicant convened for adjudication as to whether they were probably or possibly cases of IC (or whether there was insufficient evidence to reach a conclusion) The panel consisted of five gastroenterologists, all of whom are considered experts in the field of IBS.:

- Only the 3 original cases of IC present in the linaclotide database were rated as "probable" cases of IC. Two of these 3 patients were receiving linaclotide at the time of the AE; the third experienced the event 12 days following cessation of linaclotide dosing. All 3 were typical cases of reversible IC, occurring in older patients (age ≥ 64 years) with several IC-related risk factors of vascular and cardiovascular disease.

- The remaining 11 Cases of Interest were considered by the majority (5 of 5 or 4 of 5 experts) of Expert Panelists to have insufficient evidence to support the diagnosis of IC.

For each of the 3 Cases of Interest considered probable IC, the majority 5 of 5 or 4 of 5 experts) of panel members concluded that the event was probably not related to study drug.

The total exposure to linaclotide across the entire clinical development program was 3643. Based on the occurrence of 3 cases of probable IC in patients who received linaclotide, the incidence rate of IC in patients treated with linaclotide is 82.3 per 100,000 PY. The observed incidence of IC in linaclotide patients is similar to estimates from large population-based cohort studies; 79.84 per 100,000 PY in IBS patients and 68.91 per 100,000 PY in constipation patients. (Suh et al, 2007)¹¹.

Table 62: Summary of Ischemic Colitis SAE Reports

Trial/ Site	Patient ID/ Age/Sex	Indication/ Dose	Dates of drug use	Date of AE	Comments
MCP103- 305/ 028	0542012/ 62/F	IBS-C/ 290ug ¹	3/18/2010 9/16/2011	9/16/2011	ischemic colitis by clinical picture and biopsy + risk factors
LIN- MD02/ 003	0033120/ 71/F	IBS-C/ 145 ug ²	3/18/2010 4/15/2011	4/15/2011	Preferred terms ileus, colitis ulcerative ³ + risk factors
MCP-103- 201 020	020007 74/M	CIC/ 290ug	4/17/2007 4/30/2007	5/10/2007	Occurred 10 days after drug discontinued. + risk factors

1 Equivalent to 300 ug

2 Equivalent to 150 ug

3 The Investigator initially reported the event as “symptomatic ischemic colitis,” but changed it to “ileus secondary to ischemic ulcerative colitis” one day later. This Investigator Term was split into two terms for coding, initially as Preferred Terms “ileus” and “colitis ulcerative” but subsequently, based on the clinical picture, to Preferred Terms “ileus” and “colitis ischemic.”

Case #1 – 0542012

This is a 62-year-old, white female with irritable bowel syndrome with constipation, vascular and cardiovascular disease, who was treated with linaclotide 290µg/day (548 days from 18 Mar 2010 to 16 Sep 2011). This patient was screened for study MCP-103-302 but was randomization- ineligible and therefore received no investigational product in that lead-in study.

On 16 Sep 2011 (Study Day 548), the patient experienced the AE of colitis ischemic, which was upgraded to an SAE on 17 Sep 2011 (Study Day 549). The SAE of colitis ischemic prompted permanent discontinuation of linaclotide and was reported to have resolved on 30 Sep 2011, 14 days after linaclotide discontinuation.

Per MedWatch, on 16 Sep 2011, the patient experienced worsening constipation and gave herself a tap-water enema. On [REDACTED] (b) (6) days after starting linaclotide, the patient began to experience abdominal cramping, and abdominal pain, which was rated a 10 on a 1 to 10 point scale. Later in the morning, the patient experienced bloody diarrhea, nausea, and vomiting, and went to the emergency room (ER) for evaluation. While in the ER, she did not appear to be in acute distress. The patient was afebrile with stable vital signs. A physical exam of her abdomen revealed lower abdominal tenderness without guarding or rebound; no masses were palpated and no abdominal bruits were heard. Laboratory test results from [REDACTED] (b) (6) included hemoglobin of 10.4 g/dL (normal range: 11.5-15.5), hematocrit of 30.5% (normal range 35.0-47.0), white blood count of 23 x 10⁹/L (normal range: 3.50-11.10), platelet count of 252, lactic acid of 2.4 (units and normal range not specified), sodium 133 mEq/L (normal range: 134-136), BUN 30 mg/dL (normal range: 9-24), and creatinine 1.3 mg/dL (normal range: 0.5-1.0). Stool cultures (prior to antibiotic therapy) and stool testing for Clostridium difficile toxin, Campylobacter antigen, cryptosporidium; and Giardia from [REDACTED] (b) (6) were all negative. A computed tomography (CT) scan with contrast on the same day showed thickening of the transverse- and descending-colon segments; there was no free air or portal venous gas. Impressions from the [REDACTED] (b) (6) evaluations included acute colitis with bloody diarrhea, (ischemic versus infectious, doubt inflammatory); chronic constipation; and leukocytosis secondary to the acute colitis. The patient was placed on a clear liquid diet and treated with Dilaudid (hydromorphone) using patient-controlled analgesia and Flagyl (metronidazole). On 18 Sep 2011, laboratory test results were within normal range with the exception of white blood count of 19.1 x 10⁹/L (normal range: 3.50- 11.10), and neutrophil percentage of 86.4 (normal range: 40.0-74.0). Blood cultures from 18 Sep 2011 showed no growth at 5 days. On 19 Sep 2011, flexible sigmoidoscopy and sigmoid biopsy confirmed ischemic colitis of the sigmoid colon. Additional medication treatments included Levaquin (levofloxacin), Phenergan (promethazine), Vicodin (hydrocodone & acetaminophen), pantoprazole, Zofran (ondansetron), and intravenous (IV) fluids. An abdominal exam on 20 Sep 2011 revealed a soft, non-tender abdomen with no masses, and normal bowel sounds. A review of systems was positive for loose stools. Dilaudid (hydromorphone) and Flagyl (metronidazole) were discontinued on [REDACTED] (b) (6) the day the patient was discharged home. Discharge instructions included a regular diet and Levaquin starting on 21 Sep 2011 for five days. The patient was scheduled for follow-up with her primary care physician. Follow-up laboratory test results from 22 Sep 2011 included a normal white blood count of 8.69 x 10⁹/L (normal range: 3.5-11.10). All remaining laboratory test results were within normal range with the exception creatinine of 1.2 mg/dL (normal range: 0.5-1.0).

Linaclotide therapy was discontinued on 16 Sep 2011 and was not resumed. The patient had her final early termination/end of study site visit (V9) on 22 Sep 2011. On 30 Sep 2011, the SAE of ischemic colitis was considered to have resolved with no sequelae. The Investigator considered the SAE of colitis ischemic to be severe in intensity and possibly related to linaclotide.

The patient's relevant medical history included normal colonoscopy and colon polyps in February 2010, hypertension, hypercholesterolemia, coronary artery disease, and status post angioplasty x3.

Additional relevant concomitant medications included aspirin, amlodipine, benazepril, diltiazem, simvastatin, and rosuvastatin.

Case #2 – 0033120 – Trial LIN-MD-02

71-year-old, white female with irritable bowel syndrome with constipation who was initially treated with linaclotide 290 µg/day (386 days from 26 Mar 2010 to 15 Apr 2011). This patient was screened for Study LIN-MD-31 but was randomization-ineligible and therefore received no investigational product in that lead-in study.

On 04 Apr 2010 (Study Day 10), the patient experienced the adverse events (AEs) of defecation urgency, diarrhea, and fecal incontinence which prompted a reduction of the dose of linaclotide administered on 04 Apr 2010. On 22 Dec 2010 (Study Day 272), the patient experienced the SAE of cystocele which on 11 Apr 2011 prompted a temporary suspension of linaclotide treatment immediately prior to a surgical procedure to repair her cystocele. On 01 Feb 2011 (Study Day 313), the patient experienced the AE of urinary tract infection. On [REDACTED] (b) (6) the patient experienced the AEs of enterocele and rectocele which also were associated with a temporary suspension of linaclotide treatment prior to the surgical procedure to repair these abnormalities. On 15 Apr 2011 (Study Day 386), the patient experienced the AE of procedural pain. On 16 Apr 2011 (Study Day 387), the patient experienced the AEs of abdominal pain and ulcerative colitis (ischemic ulcerative colitis) and the SAE of ileus. The SAE of ileus prompted permanent discontinuation of linaclotide on 15 Apr 2011.

Per MedWatch, on 22 Dec 2010, the patient reported that her prolapsed bladder was increasingly problematic. On [REDACTED] (b) (6), the patient was hospitalized for repair of her cystocele. Pre-operative physical examination was notable for an enterocele. On [REDACTED] (b) (6) the patient underwent enterocele Prolift and tension-free sling placement under general anesthesia. Treatment with linaclotide was temporarily interrupted from [REDACTED] (b) (6) to [REDACTED] (b) (6). The patient was discharged from the hospital on [REDACTED] (b) (6) and therapy with linaclotide was resumed. From [REDACTED] (b) (6) to 15 Apr 2011, the patient experienced pain postoperatively which was treated with hydrocodone and vicodin. A few days after discharge, the patient began to experience abdominal pain and constipation. The patient had not had a bowel movement in over a week and she

started to experience nausea, vomiting, and bloating. On [REDACTED] (b) (6) the patient was readmitted to the hospital with these complaints. Relevant diagnostic tests included an abdominal x-ray on [REDACTED] (b) (6) which showed dilated loops of large bowel. Relevant laboratory test results (date not specified) included: white blood cell count 12,200 with 74% polys, hemoglobin 12.4, hematocrit 38.2, On 17 Apr 2011, and the impression from a gastroenterology consultant was that her clinical picture was secondary to post-operative ileus related to underlying constipation. The patient's treatment consisted of bowel rest (NPO, nasogastric tube placement, and intravenous [IV] fluid support), IV metoclopramide, piperacillin/tazobactam, and pain management with hydromorphone and dicyclomine. An abdominal x-ray (2 views) was obtained on 18 Apr 2011, which showed dilated loops of the large bowel (sigmoid colon). An incomplete colonoscopy was performed on [REDACTED] (b) (6) which showed formed stool; probable obstruction of the sigmoid colon which was not well-visualized due to the presence of stool (and therefore led to the termination of the procedure); and colonic polyps, which were not resected. The patient was prepped again for a repeat colonoscopy, performed on [REDACTED] (b) (6) which showed severe ulcerations in the descending colon at 25 and 35 cm from the anus that appeared to the gastroenterologist to be due to ischemic colitis. These were biopsied, as well as intervening normal-appearing descending colon, for evaluation. Other findings included a 3 cm sigmoid polyp (not resected) and a normal-appearing proximal colon. The gastroenterologist's recommendations included treatment with Boost, a full liquid diet, the withholding of aspirin or anticoagulants for 5 days, Florastor (*saccharomyces boulardii*), removal of the nasogastric tube, and a CT angiogram. Surgical pathology results from [REDACTED] (b) (6) included the following microscopic diagnoses: fibrinopurulent exudate consistent with ulcer and/or ischemic necrosis, without colonic mucosa, dysplasia or malignancy in the hot biopsy sample from the lesion at 25 cm; acute colitis with ulcer and fibrinopurulent exudate compatible with ischemic colitis, negative for dysplasia or malignancy in the hot biopsy sample labeled to be from 45 cm; and partially denuded polypoid fragments of colonic mucosa with extensive cauterization artifact, negative for dysplasia or malignancy in the hot biopsy sample from the descending colon. A CT angiogram of the abdomen and pelvis with and without IV contrast was obtained on [REDACTED] (b) (6), the results of which showed no acute vascular changes; increased density in the mesenteric fat; generalized thickening of the wall of the colon from the transverse to sigmoid colon segments; which was interpreted to be compatible with generalized inflammatory bowel disease involving the large bowel. The patient was discharged from the hospital on [REDACTED] (b) (6). The conclusion at discharge was that the patient had colitis with ulceration, possibly irritated by constipation after treatment with pain medications. She was seen on 02 May 2011 for an early termination visit.

The AEs of defecation urgency, diarrhea, and fecal incontinence were ongoing. The AE of urinary tract infection resolved on 28 Feb 11. The SAE of cystocele and the AEs of enterocele and rectocele resolved on 11 Apr 2011. The AE of procedural pain was ongoing; the AEs of abdominal pain and ulcerative colitis and the SAE of ileus resolved on 22 Apr 2011.

The Investigator considered the AEs of defecation urgency, diarrhea, and fecal incontinence to be moderate in intensity and definitely related to linaclotide. The Investigator considered the SAE of cystocele to be severe in intensity and unrelated to linaclotide, the AEs of urinary tract infection and enterocele to be moderate in intensity and unlikely to be related to linaclotide, and the AE rectocele to be moderate in intensity and unrelated to linaclotide. The Investigator considered the AE of procedural pain to be moderate in intensity and unrelated to linaclotide, the AE of abdominal pain to be moderate in intensity and possibly related to linaclotide, the AE of ulcerative colitis to be severe in intensity and unlikely related to linaclotide, and the SAE of ileus to be severe in intensity and possibly related to linaclotide.

The patient's relevant medical history included appendectomy, appendicitis, bladder prolapse, colonic polyp, coronary angioplasty, and coronary arterial stent insertion, coronary artery disease, cystocele repair, ulcer, hyperlipidemia, hypertension, hypertriglyceridemia, hysterectomy, impaired fasting glucose, intermittent claudication, micturition urgency, peripheral vascular disorder, Raynaud's phenomenon, uterine neoplasm, and uterine rupture. The patient's other relevant concomitant medications included, acetylsalicylic acid, Anacin (aspirin/caffeine), bisacodyl, ciprofloxacin, docusate sodium, estradiol, ondansetron, simvastatin, tolterodine, and Zestoretic (lisinopril/hydrochlorothiazide).

Case #3 – 20007 – MCP-103-201

This 74 year-old, white male with CIC was enrolled in MCP-103-201, the double-blind, placebo-controlled, phase 2 study of linaclotide in CIC patients. He was treated with linaclotide (290 ug) beginning 17 Apr 2007, taking his last dose on 30 Apr 2007 (missing one dose on 23 April 2007), and withdrawing from the study on 01 May 2007 because of lack of efficacy. He was reported to have developed the adverse event of ischemic colitis on 12 May 2007.

This is likely a case of ischemic colitis. The patient was noted to have the onset of sharp severe mid-abdominal pain approximately [REDACTED] (b) (6) after his last dose of study drug. At that time, the patient also had a hard bowel movement with a small amount of bleeding per rectum. About 2 days later, after administering a Fleet's enema, he experienced dull abdominal pain that was associated with the passage of dark red blood. His abdominal pain persisted until he was seen by the Investigator. The Investigator's impression at this time was that ischemic colitis needed to be ruled out, and a flexible sigmoidoscopy was then performed, which revealed colitis of the distal colon at about 30-40 cm. The Investigator's clinical impression was further confirmed by a mucosal biopsy, which was interpreted as being consistent with ischemic colitis. Of note, the patient had a normal colonoscopy 2 yrs earlier, during an evaluation for occult blood in the stool. The patient did well after outpatient treatment with polyethylene glycol. A repeat colonoscopy was done on [REDACTED] (b) (6) which showed no evidence of colitis; biopsies taken throughout

the colon were normal. The Investigator reported that the adverse event resolved on this date.

This patient had several risk factors for ischemic colitis including advanced age, CIC, a history of hyperlipidemia, and treatment with lovastatin and aspirin. These recognized confounding factors and perhaps the administration of the Fleet's enema are likely to have contributed to this event. There is no evidence to indicate the short course of linaclotide contributed to it.

Diarrhea

Medical Officers Comment's:

Diarrhea is the most common AE, the one most often associated with withdrawal or dose reduction. The incidence of diarrhea was approximately 15% in the placebo controlled trials. In the long term safety trials 32% of patients required dose reduction, with the majority of these being secondary to diarrhea. Of the patients who had dose reduction, one-half were subsequently discontinued and one-half were able to continue linaclotide with reported efficacy. While there was no evidence of difference of in the incidence of diarrhea between the two doses in the CIC trials, the higher doses used in the phase 2 dose ranging trials were associated with an increase in diarrhea.

Combining this information with the fact that half of the patients requiring dose reduction in the long term safety trials were able to tolerate a lower dose without diarrhea and the fact that diarrhea was the most common reason for discontinuation in the phase 3 trials; leads to the conclusion that the higher dose may be associated with an increased incidence of diarrhea. However, the data from the phase 3 CIC trials did not show a significant difference in diarrhea between the two doses.

Drug-Demographic data is analyzed by the applicant for the Phase 3 placebo-controlled trials only. In general, increased age (>65y) increased the incidence of AE's of diarrhea, by approximately 5% over the younger patients. There was also increased diarrhea in the male CIC population but not the male IBS-C population. Diarrhea AE's occurred more frequently in linaclotide treated Caucasian patients (17.1%), than in linaclotide treated Black patients (7.6%). See discussion in Section 7.5.3 Drug-Demographic Interactions on page 199.

Diarrhea is the most common AE, and was the TEAE associated with the highest incidence of withdrawal.

Group 1 – Phase 3 Controlled Trials – Pooled IBS-C and CIC Patients

In the Group 1 CIC population, 69 (16.0%) patients in the linaclotide 145 ug/day group and 60 (14.2%) patients in the linaclotide 290 ug/day groups experienced at least 1

episode of diarrhea vs. 20 (4.7%) placebo patients. None of the TEAEs of diarrhea were reported as SAEs, although diarrhea was reported in one patient along with the TEAEs of dehydration and orthostatic hypotension that were reported as serious. A total of 15 (1.8%) CIC linaclotide patients had diarrhea TEAEs that were reported as severe vs. 1 (0.2%) placebo patient. A total of 36 (4.2%) linaclotide patients discontinued from the Phase 3 placebo-controlled trials because of a TEAE of diarrhea versus 2 (0.5%) placebo patients. There were no clinically relevant differences in the incidence of diarrhea TEAEs, severe diarrhea TEAEs, or diarrhea ADOs between the 2 linaclotide dose groups.

Similar results were obtained in the Group 1 IBS-C patient population. These data are summarized in Table 8.6.2.1.1–2; 160 (19.8%) linaclotide patients experienced at least 1 episode of diarrhea vs. 24 (3.0%) placebo patients. None of the TEAEs of diarrhea were reported as SAEs. A total of 16 (2.0%) linaclotide patients had diarrhea TEAEs that were reported as severe vs. 1 (0.1%) placebo patient. A total of 43 (5.3%) linaclotide patients discontinued from the phase 3 placebo-controlled trials because of a TEAE of diarrhea versus 3 (0.4%) placebo patients.

Phase 3 long-term trials (Group 3)

Diarrhea was reported as an AE in 29.0% of both CIC and IBS-C patients. Severe diarrhea was reported in 3.4% of CIC and 3.0% of IBS-C patients in the long-term trials.

Phase 3 placebo-controlled and long-term trials (Group 4S)

Diarrhea occurred in 32.6% of all Phase 3 linaclotide exposed patients.

Time to Onset of Diarrhea

Among the CIC patients experiencing a TEAE of diarrhea, the time (mean \pm SD) from the first dose of double-blind treatment to the first TEAE of diarrhea was 16.4 ± 20.5 days (median = 6) for the linaclotide patients compared with 30.9 ± 29.1 days (median = 17) for the placebo patients. Of the 129 CIC linaclotide patients who had TEAEs of diarrhea, 68 (52.7%) experienced their first episode in the first week of treatment. See Table 63.

Table 63: Incidence of AE of Diarrhea in CIC Patients in the Phase 3 Placebo-Controlled Trials (Group 1) by Time of Onset of First Occurrence— Safety Population

	Placebo (N = 423)		Linaclotide					
			145 ug/day (N = 430)		290 ug/day (N = 422)		Total (N = 852)	
	n (%) ^a	Cumulative n (%) ^b	n (%) ^a	Cumulative n (%) ^b	n (%) ^a	Cumulative n (%) ^b	n (%) ^a	Cumulative n (%) ^b
Patients with diarrhea AE	20 (4.7)	—	69 (16.0)	—	60 (14.2)	—	129 (15.1)	
Time of initial onset of diarrhea								
Day 1	0	0	16 (3.7)	16 (23.2)	13 (3.1)	13 (21.7)	29 (3.4)	29 (22.5)
Day 2	4 (0.9)	4 (20.0)	10 (2.3)	26 (37.7)	7 (1.7)	20 (33.3)	17 (2.0)	46 (35.7)
Days 3-7	0	4 (20.0)	10 (2.3)	36 (52.2)	12 (2.8)	32 (53.3)	22 (2.6)	68 (52.7)
Week 2	4 (0.9)	8 (40.0)	10 (2.3)	46 (66.7)	6 (1.4)	38 (63.3)	16 (1.9)	84 (65.1)
Week 3	3 (0.7)	11 (55.0)	5 (1.2)	51 (73.9)	3 (0.7)	41 (68.3)	8 (0.9)	92 (71.3)
Week 4	1 (0.2)	12 (60.0)	5 (1.2)	56 (81.2)	5 (1.2)	46 (76.7)	10 (1.2)	102 (79.1)
Week 5	1 (0.2)	13 (65.0)	0	56 (81.2)	6 (1.4)	52 (86.7)	6 (0.7)	108 (83.7)
Week 6	0	13 (65.0)	2 (0.5)	58 (84.1)	3 (0.7)	55 (91.7)	5 (0.6)	113 (87.6)
Week 7	1 (0.2)	14 (70.0)	2 (0.5)	60 (87.0)	0	55 (91.7)	2 (0.2)	115 (89.1)
Week 8	3 (0.7)	17 (85.0)	3 (0.7)	63 (91.3)	2 (0.5)	57 (95.0)	5 (0.6)	120 (93.0)
Week 9	0	17 (85.0)	1 (0.2)	64 (92.8)	2 (0.5)	59 (98.3)	3 (0.4)	123 (95.3)
Week 10	0	17 (85.0)	0	64 (92.8)	1 (0.2)	60 (100)	1 (0.1)	124 (96.1)
Week 11	1 (0.2)	18 (90.0)	3 (0.7)	67 (97.1)	0	60 (100)	3 (0.4)	127 (98.4)
Week 12 and later	2 (0.5)	20 (100)	2 (0.5)	69 (100)	0	60 (100)	2 (0.2)	129 (100)

a For percentages within a given time period (Day 1, Day 2, Days 3-7, Week 2, etc.) the denominator is the safety population for that dose group.

b For cumulative percentages, the denominator is the number of patients with a TEAE of diarrhea for that dose group.

Similar results were obtained in the IBS-C patients. The time (mean ± SD) from the first dose of double-blind treatment to the first TEAE of diarrhea was 20.7 ± 31.7 days (median = 7.5) for the linaclotide patients compared with 43.5 ± 40.4 days (median = 22) for the placebo patients. Of the 160 IBS-C linaclotide patients who had TEAEs of diarrhea, 80 (50.0%) experienced their first episode in the first week of treatment. See Table 64.

Diarrhea Duration

Medical Officer's Comments:

There was considerable variation in the longest duration of diarrhea in each treatment group; it varied from 1 day to more than 28 days. Duration of diarrhea did not appear to be dose-related.

There was considerable variation in the longest duration of diarrhea in each treatment group; it varied from 1 day to more than 28 days. Duration of diarrhea did not appear to be dose-related. In 58 (45.0%) of the 129 linaclotide CIC patients who reported diarrhea (vs. 15 [75%] placebo patients), and in 49 (30.6%) of the 160 linaclotide IBS-C patients who reported diarrhea (vs. 13 [54.2%] placebo patients), the events resolved within 7 days in patients who continued to take double-blind treatment. See

Table 65 and Table 66.

Table 64: Duration of Diarrhea TEAEs in CIC Patients in the Phase 3 Placebo-Controlled Trials (Group 1)—Safety Population

	Placebo (N = 798)		Linaclotide 290 ug/day (N = 807)	
	n (%) ^a	Cumulative n (%) ^b	n (%) ^a	Cumulative n (%) ^b
Patients with diarrhea AE	24 (3.0)		160 (19.8)	—
Time of initial onset of diarrhea				
Day 1	0	0	45 (5.6)	45 (28.1)
Day 2	2 (0.3)	2 (8.3)	19 (2.4)	64 (40.0)
Days 3-7	1 (0.1)	3 (12.5)	16 (2.0)	80 (50.0)
Week 2	2 (0.3)	5 (20.8)	20 (2.5)	100 (62.5)
Week 3	7 (0.9)	12 (50.0)	12 (1.5)	112 (70.0)
Week 4	1 (0.1)	13 (54.2)	8 (1.0)	120 (75.0)
Week 5	0	13 (54.2)	11 (1.4)	131 (81.9)
Week 6	1 (0.1)	14 (58.3)	4 (0.5)	135 (84.4)
Week 7	3 (0.4)	17 (70.8)	5 (0.6)	140 (87.5)
Week 8	0	17 (70.8)	3 (0.4)	143 (89.4)
Week 9	0	17 (70.8)	2 (0.2)	145 (90.6)
Week 10	0	17 (70.8)	1 (0.1)	146 (91.3)
Week 11	0	17 (70.8)	1 (0.1)	147 (91.9)
Week 12 and later	7 (0.9)	24 (100)	13 (1.6)	160 (100)

- a For percentages occurring within a given time period (Day 1, Day2, Days 3-7, Week 2, etc.) the denominator is the safety population for that dose group.
- b For cumulative percentages, the denominator is the number of patients with a TEAE of diarrhea for that dose group.

Table 65: Duration of Diarrhea TEAEs in CIC Patients in the Phase 3 Placebo-Controlled Trials (Group 1)—Safety Population

Longest Duration of Diarrhea	Number (%) of Patients			
	Placebo (N = 423)	Linaclotide		
		145 ug/day (N = 430)	290 ug/day (N = 422)	Linaclotide Total (N = 852)
1 day	4 (0.9)	9 (2.1)	5 (1.2)	14 (1.6)
2 days	6 (1.4)	3 (0.7)	5 (1.2)	8 (0.9)
3-7 days	5 (1.2)	18 (4.2)	18 (4.3)	36 (4.2)
8-14 days	1 (0.2)	7 (1.6)	7 (1.7)	14 (1.6)
15-28 days	1 (0.2)	12 (2.8)	5 (1.2)	17 (2.0)
> 28 days	3 (0.7)	10 (2.3)	5 (1.2)	15 (1.8)
Ongoing	0	10 (2.3)	15 (3.6)	25 (2.9)
Total	20 (4.7)	69 (16.0)	60 (14.2)	129 (15.1)

For patients with multiple episodes of diarrhea the episode with the longest duration is included in this table.
 For percentages, the denominator is the safety population for that dose group

Table 66: Duration of Diarrhea TEAEs in IBS-C Patients in the Phase 3 Placebo- Controlled Trials (Group 1)—Safety Population

Longest Duration of Diarrhea	Number (%) of Patients	
	Placebo	Linaclotide 290 ug/day
1 day	5 (0.6)	14 (1.7)
2 days	3 (0.4)	9 (1.1)
3-7 days	5 (0.6)	26 (3.2)
8-14 days	2 (0.3)	11 (1.4)
15-28 days	1 (0.1)	16 (2.0)
> 28 days	6 (0.8)	50 (6.2)
Ongoing	2 (0.3)	34 (4.2)
Total	24 (3.0)	160 (19.8)

For patients with multiple episodes of diarrhea the episode with the longest duration is included in this table.
 For percentages, the denominator is the safety population for that dose group.

Severe diarrhea has the potential to cause alterations in electrolytes. Therefore, special attention was paid to changes in serum electrolytes in the subgroup of patients who reported the TEAE diarrhea. In the CIC population of the double-blind, placebo-controlled studies (Group 1), 129 linaclotide and 20 placebo patients had a TEAE of

diarrhea. Three (2.4%) of 127 linaclotide patients for whom data were available, had shifts in bicarbonate from normal to low; 1 (0.8%) of 121 linaclotide patients had a shift in potassium from normal to low; and 1 (0.8%) of 121 linaclotide patients had a shift in potassium from normal to high. None of the CIC placebo patients with diarrhea had a shift from normal in any of the electrolytes analyzed.

In the IBS-C population, 160 linaclotide and 24 placebo patients had a TEAE of diarrhea. Seven (4.5%) of 156 linaclotide patients for whom data were available, had shifts in bicarbonate from normal to low (vs. 0 of 24 placebo patients); 6 (4.0%) of 149 linaclotide patients had shifts in potassium from normal to low (vs. 1 [4.8%] of 21 placebo patients); 2 (1.3%) of 149 linaclotide patients had shifts in potassium from normal to high (vs. 0 of 21 placebo patients); and 1 (0.6%) of 157 linaclotide patient had a shift in sodium from normal to low (vs. 1 [4.2%] of 24 placebo patients).

Severe diarrhea can cause intravascular volume depletion. Since diarrhea is the most common adverse event in patients treated with linaclotide, it was thought important to assess whether excessive fluid loss via the GI tract might be occurring in patients, with likely manifestations being AEs of dehydration, dizziness, and orthostatic hypotension. Therefore, special attention was paid in the assessment of these adverse events.

Dehydration

Medical Officer's Comments:

Dehydration occurred in less than 0.5% of all patients treated with linaclotide during the Phase 3 clinical trials, and when it occurred, it occurred primarily in patients with diarrhea. The overall incidence of dehydration is low; however it is more prevalent in the treatment group and slightly increased with the higher dose.

CIC patients

In the Phase 3 placebo-controlled CIC trials (Group 1), dehydration was reported by no patients on placebo, by 2 (0.5%) patients on linaclotide 145 ug, and by 4 (0.9%) patients on linaclotide 290 ug. In the patients with dehydration, diarrhea was reported as a TEAE in 1 of the 2 patients receiving linaclotide 145 ug and in 3 of the 4 patients receiving linaclotide 290 ug.

Two patients (830102 and 1190106) receiving linaclotide 290 ug discontinued from the study because of the ADO dehydration; both had concurrent diarrhea reported as TEAEs.

A third patient (0570150) receiving linaclotide 290 ug had the SAEs dehydration and orthostatic hypotension; this patient was a 34-year-old woman who presented with nausea, vomiting, hypoglycemia, dizziness, orthostatic hypotension, and dehydration. The patient reported only a single episode of diarrhea that was not severe, and that

occurred earlier on the day of her visit to the health center for the above symptoms. The patient later resumed linaclotide treatment without recurrence of the symptoms.

One patient (290102) receiving linaclotide 145 ug withdrew from the study because of the ADO diarrhea and had concurrent dehydration reported as a TEAE.

One (patient 473003; linaclotide 290 ug) of the 2 CIC patients with dehydration and no diarrhea had the SAE “cerebrovascular accident”, which was associated with the concurrent AE, azotemia. The other patient (153008; linaclotide 145 ug) had dehydration that lasted for one day and reported no other AEs.

IBS-C Patients

In the Phase 3 placebo-controlled IBS-C trials (Group 1), dehydration was reported by 2 (0.3%) patients on placebo and by 2 (0.2%) patients on linaclotide 290 ug. In the patients with dehydration, diarrhea was reported as a TEAE in neither of the 2 patients receiving placebo ug and by 1 of the 2 patients receiving linaclotide 290 ug. In the patient (192007) with diarrhea and dehydration, the diarrhea antedated the dehydration (which lasted 2 days) by 4 months.

Dizziness

Medical Officer’s Comments:

Similar to dehydration, the incidence of dizziness is low; however it is more prevalent in the treatment group and slightly increased with the higher dose.

CIC Patients

In the Phase 3 placebo-controlled CIC trials (Group 1), dizziness was reported by 2 (0.5%) patients on placebo, by 4 (0.9%) patients on linaclotide 145 ug, and by 6 (1.4%) patients on linaclotide 290 ug. In the patients with dizziness, diarrhea was reported as a TEAE in 0 of the 2 patients receiving placebo, by 0 of 4 patients receiving linaclotide 145 ug, and by 3 of the 6 patients receiving linaclotide 290 ug.

Two of the 3 patients with dizziness and diarrhea also reported dehydration as a TEAE (as an ADO in patient 1190106 and as an SAE in patient 570150). The third patient (1093010) reported dizziness concurrently with diarrhea, nausea, and vomiting, each of which resolved within 5 days; this patient also reported dizziness that was not associated with diarrhea.

IBS-C Patients

In the Phase 3 placebo-controlled IBS-C trials (Group 1), dizziness was reported by 10 (1.3%) patients on placebo and by 10 (1.2%) patients on linaclotide 290µg. In the patients with dizziness, diarrhea was reported as a TEAE in 1 of the 10 patients receiving placebo and by 3 of the 10 patients receiving linaclotide 290µg. One patient

(632051) withdrew from a study because of dizziness that occurred concurrently with diarrhea.

Orthostatic hypotension

Medical Officer's Comments:

Orthostatic hypotension was rare in the phase 3 trials, occurring in association with diarrhea, nausea and vomiting.

CIC Patients

In the Phase 3 placebo-controlled CIC trials (Group 1), orthostatic hypotension occurred in no patients on placebo, in 1 (0.2%) patient on linaclotide 145µg, and in 2 (0.5%) patients on linaclotide 290 µg. In the patients with orthostatic hypotension, diarrhea was not reported as a TEAE in the patient receiving linaclotide 145µg but was reported in 1 of the 2 patients receiving linaclotide 290µg. The patient (140103) on the 145µg dose without diarrhea reported bronchitis as an SAE, which occurred concurrently with the orthostatic hypotension, cough, and fluid intake reduced. The patient (0570150) on the 290 µg dose with diarrhea reported dehydration and orthostatic hypotension as SAEs and was discussed above in the Dehydration Section. The patient (600103) on the 290µg dose without diarrhea reported orthostatic hypotension that lasted for 9 days and did not occur in association with any other TEAE.

IBS-C Patients

In the phase 3 placebo-controlled IBS-C trials (Group 1), orthostatic hypotension was not reported as an AE.

In summary, dehydration occurred in less than 0.5% of all patients treated with linaclotide during the phase 3 clinical trials, and when it occurred, it occurred primarily in patients with diarrhea and at rates that were low (less than 4% of all patients with diarrhea). Dizziness occurred in less than 1.5% of patient treated with placebo or linaclotide; most patients with dizziness did not experience diarrhea and less than 4% of all patients with diarrhea experienced dizziness. Orthostatic hypotension occurred very uncommonly during the Phase 3 clinical trials; in two of the three cases where it clearly occurred, there was an alternative explanation (e.g., nausea, vomiting, reduced fluid intake) for its occurrence.

Biliary Disease (Group 4)

Medical Officer's Comments:

There were several cases of biliary disease in the open-label long-term safety trials, however the incidence was equal to the expected incidence of biliary disease in this population.

In the phase 3 placebo-controlled trials, 2 linaclotide patients reported gallstones (cholelithiasis). In the LTS studies, by the cut-off date of 11-Oct-2010, 11 cases of gallstones (10 cholelithiasis, 1 bile duct stone, [2 with pancreatitis]), 5 cases of gallbladder dyskinesia, and 2 cases of gallbladder cholesterosis were reported. Therefore, the total number of known gallbladder disease cases among all linaclotide patients was 20. In order to assess whether linaclotide increases the risk of gallbladder disease, the incidence in linaclotide recipients was compared with incidence rates from the literature.

The Applicant submitted the following supporting data and evaluation. In a population based study in Italy, Corazziari et al. compared the prevalence of gallbladder disease in a group of IBS patients, a group of subjects with abdominal pain but no IBS, a group of subjects with altered bowel habits but no abdominal pain and a group of control subjects.¹² They found that subjects with IBS may have an increase risk of cholecystectomy, but not of gallstones. After following a subset (3636 female and 4824 male subjects) of their cross-sectional study population for an average of 7.8 years, they found 212 new cases of “gallstone disease” (defined as gallstones confirmed by ultrasound, or cholecystectomy) in females and 204 in males; this represents an incidence rate of approximately 748/100,000 person-years in females and 542/100,000 person-years in males. In phase 2 and 3 studies, the total exposure to linaclotide was 2838 person-years (group 4). Applying the incidence rates of the Italian study to the linaclotide study population, adjusting for gender, a total of 21.2 cases of “gallstone disease” would be expected in linaclotide recipients, where 20 were observed. Linaclotide does not seem to increase the risk of gallbladder disease.

The data presented in the 120-day Safety Update include an additional 8 months of integrated safety information, from 12-Oct 2010 thru 11-Jun-2011, on CIC and IBS-C patients who were enrolled in an ongoing LTS study. During this period, CIC patients had an additional 63 patient-years of exposure to linaclotide and IBS-C patients had an additional 746 patient-years of exposure. The 120-day safety update (Section 7.4 on page 167) reported four additional cases of biliary dyskinesia and four of cholecystitis.

Medical Officers Comment:

A consult was obtained from Carolyn McCloskey, MD, MPH, Epidemiologist in the Division of Epidemiology I (DEPI I), Office of Pharmacoepidemiology and Epidemiology (OPE) OSE, CDER and their conclusion was that The Italian Corazziari study is the best source for a comparator incidence rate for gallstones in IBS patients and therefore for use in the linaclotide safety study. Even though other studies report incidence rates for the general US population, it is possible that their gallstone/cholecystectomy incidence rates are lower than the Corazziari study because the Corazziari study established a truer gallstone-free group using ultrasonography. The expected number of gallbladder cases is 21 and the linaclotide safety studies had 20 cases. Their recommendation was that given the conservative estimates from Corazziari study, the linaclotide gall bladder safety finding is reassuring at this time.

7.4 Supportive Safety Results - 120-day Safety Update

Medical Officer's Comments:

The 120-day safety update revealed no significantly different information than the review of the original submission.

See discussion in also Section 7.2.2 Explorations for Dose Response on page 130. The data presented in the 120-day Safety Update include an additional 8 months of integrated safety information, from 12-Oct-2010 thru 11-Jun-2011, on CIC and IBS-C patients who were enrolled in an ongoing LTS study. During this period, CIC patients had an additional 63 patient-years of exposure to linaclotide and IBS-C patients had an additional 746 patient-years of exposure. A total of 1627 CIC and 2753 IBS-C patients were exposed to linaclotide across all 10 phase 2 and 3 studies. Total exposure of CIC patients to linaclotide was 1394 patient-years and total exposure of IBS-C patients to linaclotide was 2253 patient-years.

During the 8 months of additional treatment the TEAE profile was similar to that presented in the ISS. Increased exposure resulted in a somewhat higher incidence of TEAEs, as expected. During the 8 months between 12-Oct-2010 and 11-Jun-2011, 44 patient experienced SAEs and 42 patients discontinued due to TEAEs. No deaths were reported. Overall, no clinically meaningful mean changes were observed in clinical laboratory parameters, vital signs, or ECG parameters, and the incidences of PCS values remained low. During the additional 8 months of observation 8 more pregnancy outcomes were recorded: 6 healthy babies were delivered at term; there were also 2 abortions (1 elective and 1 spontaneous).

Table 67: Treatment-Emergent Adverse Events Reported in ≥ 5% of all CIC or IBS-C Patients in the Phase 3 Open-label Long-term Safety Studies (Group 3) —Safety Population

Adverse Event (Preferred Term)	Number (%) of Patients		
	Total CIC (N=1129)	Total IBS-C (N = 2147)	Total CIC + IBS- C (N = 3271)
Any TEAE	849 (75.2)	1554 (72.4)	2401 (73.4)
Diarrhea	358 (31.7)	693 (32.3)	1051 (32.1)
Sinusitis	71 (6.3)	137 (6.4)	208 (6.4)
Urinary tract infection	72 (6.4)	127 (5.9)	199 (6.1)
Abdominal pain	58	135 (6.3)	193 (5.9)
Upper respiratory tract infection	58 (5.1)	119 (5.5)	177 (5.4)
Nausea	64 (5.7)	105 (4.9)	169 (5.2)
Flatulence	60 (5.3)	66 (3.1)	126 (3.9)

Numbers of patients may not add up due to counting of duplicate patients. TEAEs are ordered by decreasing frequency among all patients.

CIC = chronic constipation; IBS-C = irritable bowel syndrome with constipation; TEAE = treatment-emergent adverse event.

In total, 372 (11.4%) of 3271 patients experienced an ADO during an LTS study. Most of the ADOs were gastrointestinal disorders; diarrhea was the most frequently reported ADO (5.3% of patients overall). There were no other TEAEs that resulted in the discontinuation of $\geq 1\%$ of patients overall. Most patient discontinuations were due to reasons other than TEAEs.

The incidence of SAEs remained similar to the initial report except for one notable exception in a report of a case of ischemic colitis. See discussion in Section 7.3.5 on page 151, for a discussion on ischemic colitis events. There were no SAEs of diarrhea. There were four cases each of cholecystitis and biliary dyskinesia.

7.4.1 Common Adverse Events

Medical Officer's Comments:

Overall the incidence of AE's is similar between placebo and treatment groups, except for AE's in the GI SOC which were increased in the treatment group. Diarrhea was by far the most common AE, with an incidence of about 17% in the controlled trials compared to placebo incidence of ~3.6%. Flatulence (4.8% vs 3.0%) and abdominal pain (4.7% vs 3.2%) also occurred more commonly in the treatment groups than in the placebo groups in the controlled trials.

In the long-term trials, the incidences of specific AEs differed somewhat between the 2 indications (CIC and IBS-C), possibly due to differences in exposure time to linaclotide, the types of AEs were in general similar. The most frequently reported TEAE was diarrhea (31.4% of CIC and 30.4% of IBS-C patients in the open-label studies).

Group 1 – Phase 3 Controlled Trials – Pooled CIC patients (Table 68)

Approximately 50-60% of all patients experienced at least one TEAE. The most frequently reported TEAEs were in the GI disorders, and infections and infestations SOCs. Diarrhea was the most common TEAE, occurring in 15.1% of linaclotide-treated patients and 4.7% of placebo patients. TEAE rates were similar between the 145 and 290ug linaclotide dose groups.

The reporting of TEAEs, particularly diarrhea, tended to decrease over time. Among linaclotide patients the incidence of diarrhea decreased from 12.0% in the first 4 weeks to 4.1% between treatment weeks 4 to 12 and $< 1\%$ after Week 12. The temporal occurrence of non-GI TEAEs was similar among the treatment groups.

Overall, 6.0% of linaclotide 145 ug patients and 7.3% of linaclotide 290 ug patients experienced severe TEAEs compared with 5.7% of placebo patients. The incidence of any particular severe TEAE was generally similar between the 2 linaclotide dose groups, and, except for diarrhea, between linaclotide and placebo (145ug – 1.6%, 290ug – 1.9% and placebo 0.2%).

Table 68: Treatment-Emergent Adverse Events Reported in ≥ 2% of Linaclotide CC Patients in Either Treatment Group of the Phase 3 Placebo-Controlled Trials (Group 1) and at an Incidence Greater Than Placebo—Safety Population

<i>Adverse Event (Preferred Term)</i>	<i>Number (%) of</i>			
	<i>Placebo (N = 423)</i>	<i>Linaclotide</i>		
		<i>145 ug/day (N = 430)</i>	<i>290 ug/day (N = 422)</i>	<i>Linaclotide Total (N = 852)</i>
Any TEAE	222 (52.5)	262 (60.9)	235 (55.7)	497 (58.3)
Diarrhea	20 (4.7)	69 (16.0)	60 (14.2)	129 (15.1)
Flatulence	22 (5.2)	24 (5.6)	21 (5.0)	45 (5.3)
Abdominal pain	13 (3.1)	17 (4.0)	20 (4.7)	37 (4.3)
Upper respiratory tract	17 (4.0)	22 (5.1)	13 (3.1)	35 (4.1)
Nausea	15 (3.5)	15 (3.5)	18 (4.3)	33 (3.9)
Abdominal distension	10 (2.4)	15 (3.5)	15 (3.6)	30 (3.5)
Nasopharyngitis	13 (3.1)	9 (2.1)	17 (4.0)	26 (3.1)
Sinusitis	8 (1.9)	13 (3.0)	11 (2.6)	24 (2.8)
Abdominal pain upper	7 (1.7)	13 (3.0)	5 (1.2)	18 (2.1)
Vomiting	9 (2.1)	5 (1.2)	10 (2.4)	15 (1.8)

Group 1 – Phase 3 Controlled Trials – Pooled IBS-C Patients (Table 69)

Approximately 60% of linaclotide-treated patients experienced at least one AE. With the exception of headache, all are in the GI disorders SOC and were experienced by linaclotide IBS-C patients at an incidence at least 1 percentage point more than placebo patients. Diarrhea was the most common AE experienced by linaclotide patients (19.8% vs. 3.0% of placebo patients). A further discussion of diarrhea is presented in Section 7.3.5 Submission Specific Primary Safety Concerns.

For all AEs that occurred in < 2% of linaclotide patients and at an incidence greater than placebo, the difference between linaclotide and placebo was < 1 percentage point. Thus, less common TEAEs occurred at about the same frequency with linaclotide as they did with placebo.

Overall, 7.1% of linaclotide patients experienced severe AEs compared with 3.4% of placebo patients. Diarrhea was reported as severe in greater than 1% of linaclotide patients. Of the 160 linaclotide patients who experienced AEs of diarrhea, 16 (10.0%) had events that were reported as severe, which represent 2.0% of the total population of Group 1 IBS-C patients exposed to linaclotide.

Overall, 30.1% of linaclotide-treated patients experienced related AEs compared with 14.4% of placebo patients.

Table 69: Treatment-Emergent Adverse Events Reported in $\geq 2\%$ of Linaclotide IBS-C Patients in the Phase 3 Placebo-Controlled Trials (Group 1) and at an Incidence Greater Than Placebo — Safety Population

<i>Adverse Event (Preferred Term)</i>	<i>Number (%) of</i>	
	<i>Placebo (N = 798)</i>	<i>Linaclotide 290 ug/day</i>
Any TEAE	438 (54.9)	491 (60.8)
Diarrhea	24 (3.0)	160 (19.8)
Abdominal pain	26 (3.3)	41 (5.1)
Flatulence	15 (1.9)	35 (4.3)
Headache	25 (3.1)	33 (4.1)
Gastroenteritis viral	11 (1.4)	21 (2.6)
Abdominal distension	9 (1.1)	18 (2.2)

Table 70: Treatment-Emergent Adverse Events Reported as Severe in at Least 2 Linaclotide IBS-C Patients in the Phase 3 Placebo-Controlled Trials (Group 1) Safety Population

Adverse Event (Preferred Term)	Number (%) of Patients	
	Placebo (N = 798)	Linaclotide 290 ug/day (N = 807)
Any TEAE	27 (3.4)	57 (7.1)
Diarrhea	1 (0.1)	16 (2.0)
Abdominal pain	2 (0.3)	7 (0.9)
Abdominal distension	2 (0.3)	3 (0.4)
Nausea	2 (0.3)	3 (0.4)
Flatulence	0	2 (0.2)
Headache	0	2 (0.2)
Gastroenteritis viral	0	2 (0.2)
Vomiting	0	2 (0.2)

Group 1 – Phase 3 Controlled Trials - Pooled CIC + IBS-C Patients

Approximately 60% of linaclotide-treated patients experienced at least one AE. As was true for the individual indications, the most frequently reported AEs were in the GI disorders, and infections and infestations SOCs. Although the incidences of specific AEs differed slightly between the 2 indications (CIC and IBS-C) the types of AEs were in general similar. The AEs that were experienced by at least 2% of all linaclotide patients and at an incidence at least 1 percentage point more than placebo patients were diarrhea (17.4% vs. 3.6%), flatulence (4.8% vs. 3.0%), abdominal pain (4.7% vs. 3.2%), and abdominal distension (2.9% vs. 1.6%). See Table 71

Table 71: Treatment-Emergent Adverse Events Reported in $\geq 2\%$ of All Linaclotide Patients in the Phase 3 Placebo-Controlled Trials (Group 1) and at an Incidence Greater Than Placebo Safety Population

Adverse Event (Preferred Term)	Number (%) of Patients			
	Placebo (N = 1218)	Linaclotide		
		145 ug/day (N = 430)	290 ug/day (N = 1227)	Total (N = 1657)
Any TEAE	659 (54.1)	262 (60.9)	726 (59.2)	988 (59.6)
Diarrhea	44 (3.6)	69 (16.0)	220 (17.9)	289 (17.4)
Flatulence	37 (3.0)	24 (5.6)	56 (4.6)	80 (4.8)
Abdominal pain	39 (3.2)	17 (4.0)	61 (5.0)	78 (4.7)
Headache	44 (3.6)	15 (3.5)	50 (4.1)	65 (3.9)
Abdominal distension	19 (1.6)	15 (3.5)	33 (2.7)	48 (2.9)

For TEAEs that occurred in $< 2\%$ of all linaclotide patients and at an incidence greater than placebo, the difference between linaclotide and placebo was < 1 percentage point for all AEs except: fecal incontinence (145 ug, 1.4% vs. 0.1%) and abnormal gastrointestinal sounds (290 ug, 1.1% vs. 0.1%). There were no TEAEs that met these criteria when data from both doses are combined. See Table 72.

Table 72: Treatment-Emergent Adverse Events Reported in $\geq 1\%$ and $< 2\%$ of All Linaclotide Patients in the Phase 3 Placebo-Controlled Trials (Group 1) and at an Incidence Greater Than Placebo—Safety Population

Adverse Event (Preferred Term)	Number (%) of Patients			
	Placebo (N = 1218)	Linaclotide		
		145 ug/day (N = 430)	290 ug/day (N = 1227)	Total (N = 1657)
Any TEAE	661 (54.1)	262 (60.9)	726 (59.2)	988 (59.6)
Gastroenteritis viral	13 (1.1)	8 (1.9)	23 (1.9)	31 (1.9)
Vomiting	19 (1.6)	5 (1.2)	24 (2.0)	29 (1.8)
Abdominal pain upper	19 (1.6)	13 (3.0)	15 (1.2)	28 (1.7)
Dyspepsia	14 (1.1)	8 (1.9)	13 (1.1)	21 (1.3)
Dizziness	12 (1.0)	4 (0.9)	16 (1.3)	20 (1.2)
Sinus congestion	12 (1.0)	1 (0.2)	19 (1.5)	20 (1.2)
Gastroesophageal reflux	9 (0.7)	2 (0.5)	15 (1.2)	17 (1.0)
Muscle strain	6 (0.5)	5 (1.2)	12 (1.0)	17 (1.0)

Phase 2 Double-blind Placebo-Controlled Studies (Group 2 and IBS-C Studies)

The only AEs that were experienced by at least 2% of all linaclotide patients and at an incidence at least 1 percentage point greater than that of placebo were diarrhea (8.8% vs. 2.5%) and nausea (2.9% vs. 1.3%). There was no apparent dose-relationship. Overall, the AE profile was similar to that observed in the linaclotide patients from the Phase 3 trials.

In MCP-103-005, AEs that occurred in at least 2 linaclotide patients (N = 24) were abdominal distension, abnormal bowel sounds, diarrhea, abdominal pain, flatulence, defecation urgency, headache, and somnolence. In MCP-103-202, AEs that occurred in at least 2% of 335 linaclotide patients, and at an incidence at least 1 percentage point greater than placebo were diarrhea (14.6% vs. 1.2%) and urinary tract infection (4.2% vs. 2.4%). There was a modest trend for a dose-relationship for diarrhea AEs with 11.4%, 12.2%, 16.5% and 18.0% reported in the 72, 145, 290, and 579 ug/day linaclotide treatment groups, respectively. A dose-relationship was not observed for other AEs. For the AEs of nausea, headache, abdominal distension, and flatulence, there was at least 1 percentage point greater incidence in the placebo group compared to the linaclotide group.

Group 3 - Phase 3 Open-Label Long-Term Safety Studies

The studies are still ongoing, and the results reflect only information up to the cutoff date of 11-Oct-2010. TEAEs from the lead-in studies are not included in the summary tables. The most frequently reported TEAEs were in the GI disorders, and infections and infestations SOCs. Although the incidences of specific AEs differed somewhat between the 2 indications (CIC and IBS-C), possibly due to differences in exposure time to linaclotide, the types of AEs were in general similar. The most frequently reported TEAE was diarrhea (31.4% of CIC and 30.4% of IBS-C patients in the open-label studies). See Table 73.

The majority of severe TEAEs in CIC and IBS-C patients were related to GI disorders. The most frequently reported TEAE, diarrhea, was reported as severe in 3.4% of CIC patients and 3.0% of IBS-C patients. See Table 74.

Table 73: Treatment-Emergent Adverse Events Reported in ≥ 5% of all CIC or IBS-C Patients in the Phase 3 Open-Label Long-Term Safety Studies (Group 3) — Safety Population

Adverse Event (Preferred Term)	Number (%) of Patients		
	Total CIC (N = 1129)	Total IBS-C (N = 2146)	Total CIC + IBS-C (N = 3270)
Any TEAE	839 (74.3)	1387 (64.6)	2224 (68.0)
Diarrhea	354 (31.4)	652 (30.4)	1006 (30.8)
Abdominal pain	56 (5.0)	110 (5.1)	166 (5.1)
Urinary tract infection	64 (5.7)	92 (4.3)	156 (4.8)
Sinusitis	70 (6.2)	85 (4.0)	155 (4.7)
Nausea	63 (5.6)	87 (4.1)	150 (4.6)
Flatulence	59 (5.2)	59 (2.7)	118 (3.6)

Numbers of patients may not add up due to counting of duplicate patients.
TEAEs are ordered by decreasing frequency among all patients

Table 74: Treatment-Emergent Adverse Events Reported as Severe in at Least 3 CIC or IBS-C Patients in the Phase 3 Open-Label Long-Term Safety Studies (Group 3)—Safety Population

Adverse Event (Preferred Term)	Number (%) of Patients	
	Total CIC (N = 1129)	Total IBS-C (N = 2146)
Diarrhea	38 (3.4)	64 (3.0)
Abdominal pain	7 (0.6)	21 (1.0)
Abdominal pain upper	4 (0.4)	6 (0.3)
Back pain	2 (0.2)	8 (0.4)
Headache	3 (0.3)	7 (0.3)
Abdominal distension	3 (0.3)	5 (0.2)
Flatulence	2 (0.2)	5 (0.2)
Constipation	1 (0.1)	4 (0.2)
Bronchitis	3 (0.3)	1 (0.0)
Muscle spasms	1 (0.1)	3 (0.1)
Tendonitis	1 (0.1)	3 (0.1)
Urinary tract infection	3 (0.3)	1 (0.0)
Breast cancer	0	3 (0.1)
Cystitis	3 (0.3)	0
Depression	3 (0.3)	0
Fatigue	0	3 (0.1)
Nausea	0	3 (0.1)
Nephrolithiasis	0	3 (0.1)
Upper respiratory infection	0	3 (0.1)

The events judged to be related to linaclotide treatment in at least 2% of CIC or IBS-C patients were all GI-related. See Table 75.

Table 75: Treatment-Emergent Adverse Events Reported as Related in \geq 2% of all CIC or IBS-C Patients in the Phase 3 Open-Label Long-Term Safety Studies (Group 3)—Safety Population

Adverse Event (Preferred Term)	Number (%) of Patients	
	Total CIC (N = 1129)	Total IBS-C (N = 2146)
Any TEAE	450 (39.9)	845 (39.4)
Diarrhea	327 (29.0)	623 (29.0)
Abdominal pain	34 (3.0)	88 (4.1)
Flatulence	54 (4.8)	57 (2.7)
Abdominal distension	38 (3.4)	55 (2.6)
Nausea	22 (1.9)	46 (2.1)

Group 4 – All Linaclotide Patients

Table 76: Treatment-Emergent Adverse Events Reported in ≥ 5% of CIC and IBS-C Patients Combined in the Phase 3 Placebo-Controlled or Open-Label Long-Term Safety Studies (Group 4S)—Safety Population

Adverse Event (Preferred Term)	P3 LIN RO	P3 Other	P3 Total	P2 RO	RI	Total
	N = 1522	N = 1076	N = 2598	N = 205	N = 1108	N = 3910
n (%)						
Any TEAE	1178 (77.4)	655 (60.9)	1833 (70.6)	159 (77.6)	811 (73.2)	2803 (71.7)
Diarrhea	481 (31.6)	304 (28.3)	785 (30.2)	61 (29.8)	430 (38.8)	1276 (32.6)
Abdominal pain	112 (7.4)	61 (5.7)	173 (6.7)	12 (5.9)	68 (6.1)	253 (6.5)
Nausea	103 (6.8)	41 (3.8)	144 (5.5)	18 (8.8)	61 (5.5)	223 (5.7)
Urinary tract infection	104 (6.8)	40 (3.7)	144 (5.5)	8 (3.9)	56 (5.1)	208 (5.3)
Sinusitis	114 (7.5)	25 (2.3)	139 (5.4)	25 (12.2)	48 (4.3)	212 (5.4)
Upper respiratory tract infection	121 (8.0)	32 (3.0)	153 (5.9)	19 (9.3)	39 (3.5)	211 (5.4)
Flatulence	91 (6.0)	46 (4.3)	137 (5.3)	12 (5.9)	52 (4.7)	201 (5.1)

P2 = phase 2; P3 = phase 3; LIN = linaclotide; RI = randomization ineligible; RO = rollover; TEAE = treatment-emergent adverse event.

P3 LIN RO = Patients who received linaclotide in both a Phase 3 DB study (either during the Treatment Period or the RW Period) and an open-label long-term safety study.

P3 Others = Patients who received only placebo in a Phase 3 DB study followed by Linaclotide treatment in an LTSS or received linaclotide in a Phase 3 DB study only without enrolling in an LTSS.

P3 Total = P3 LIN RO + P3 Others;

P2 RO = Patients who completed a Phase 2 study and then rolled over into an LTSS.

RI = Patients who failed to be randomization eligible in a Phase 3 DB study and then enrolled in an LTSS.
Total = P3 Total + P2 RO + RI, in which a patient who enrolled in more than 1 Group 4 study was counted once

7.4.2 Laboratory Findings

Medical Officer's Comment:

This section presents the clinical laboratory results for the Phase 3 trials and LTS studies. In these trials and in the Phase 2 studies, no clinically meaningful differences between linaclotide and placebo were observed in clinical laboratory results.

Hematology

Phase 3 Trials

The only parameter for which PCS values were reported in $\geq 2\%$ of CIC patients in any treatment group was low lymphocyte count (2.6% linaclotide 145ug/day and 2.5% linaclotide 290 ug/day vs. 1.4% for placebo). However, this imbalance was not observed in the IBS-C patients (1.3% for both linaclotide and placebo). The decrease in neutrophil count to PCS values was balanced among the treatment groups (1.4% linaclotide 145ug/day and 1.7% linaclotide 290ug/day vs. 1.9% for placebo) in the CIC trials.

There was an imbalance in increased neutrophil count for CIC patients: 0.7% of linaclotide 145ug/day and 1.2% of linaclotide 290ug/day patients, compared with 0 placebo patients.

Among the IBS-C patients the only parameter for which PCS values were recorded in $\geq 2\%$ of linaclotide patients was low neutrophil count (2.2% vs. 0.9% for placebo). However, as noted above, this imbalance was not observed in the CIC patients. In most IBS-C patients, the decrease in neutrophil count to the PCS range was transient, in that it increased to either the normal range or to the baseline value by the end of treatment. Most patients with neutrophil values in the PCS range at the end of treatment had values that were just above the PCS range at baseline. One linaclotide patient (0062020) had a neutrophil count that went from 1.8 at baseline to 0.7 at the Day 85 visit, when the patient was discontinued for the AE of white blood cell decreased. A placebo-treated CIC patient (0103017) had a neutrophil count that went from 1.6 at baseline to 0.2 at the end of the Treatment Period (Day 85); during the RW period, after the patient was placed on linaclotide 290ug, her neutrophil count increased to 1.48. See Table 77.

There were also neutrophil count increases into the PCS range for the IBS-C patients, but the rates were balanced for the 2 treatment groups (1.2% linaclotide vs. 0.9% placebo).

No notable differences were observed across the treatment groups, and no hematology TEAEs (preferred term) were reported in more than 0.5% of either CIC or IBS-C patients treated with linaclotide. None of the TEAEs were reported as SAEs. None of the CIC patients discontinued from the study because of an abnormal hematology

event. Two linaclotide IBS-C patients discontinued from the study because of a hematology TEAE (iron deficiency anemia in patient 0323110 and decreased white blood cell count in patient 0062020).

Table 77: Number (%) of Patients with Potentially Clinically Significant Hematology Parameters during the Double-blind Treatment Period of the Phase 3 Placebo-Controlled Trials (Group 1)—Safety Population

Laboratory Parameter	PCS Criteria	CIC			IBS-C Patients	
		Placebo n/N (%)	Linacotide n/N (%)		Placebo n/N (%)	Linacotide n/N (%)
			145 ug/day	290 ug/day		
Absolute eosinophil cell count	> 3 x ULN	0/418	0/423	0/412	1/774 (0.1)	0/788
Hematocrit	< 0.9 x LLN	2/415 (0.5)	1/422 (0.2)	1/410 (0.2)	3/768 (0.4)	3/783 (0.4)
	> 1.1 x ULN	0/415	0/422	0/410	0/768	2/783 (0.3)
Hemoglobin	< 0.9 x LLN	5/414 (1.2)	2/422 (0.5)	4/408 (1.0)	10/763 (1.3)	10/777 (1.3)
	>1.1 x ULN	0/414	1/422 (0.2)	0/408	0/763	0/777
Absolute lymphocyte cell count	< 0.8 x LLN	6/414 (1.4)	11/422 (2.6)	10/406 (2.5)	10/768 (1.3)	10/779 (1.3)
	> 1.5 x ULN	0/414	1/422 (0.2)	0/406	1/768 (0.1)	0/779
Mean corpuscular volume	< 0.9 x LLN	0/419	0/422	1/406 (0.2)	0/770	0/782
Absolute neutrophil cell count	< 0.8 x LLN	8/412 (1.9)	6/418 (1.4)	7/406 (1.7)	7/771 (0.9)	17/780 (2.2)
	> 1.5 x ULN	0/412	3/418 (0.7)	5/406 (1.2)	7/771 (0.9)	9/780 (1.2)
Platelet count	< 0.5 x LLN	0/419	1/421 (0.2)	0/409	1/773 (0.1)	0/780
	> 1.5 x ULN	0/419	1/421 (0.2)	0/409	3/773 (0.4)	2/780 (0.3)
Red blood cell count	< 0.9 x LLN	1/419 (0.2)	1/423 (0.2)	2/410 (0.5)	0/772	3/785 (0.4)
	> 1.1 x ULN	0/419	1/423 (0.2)	1/410 (0.2)	1/772 (0.1)	0/785
White blood cell count	< 0.7 x LLN	1/418 (0.2)	1/422 (0.2)	0/412	0/774	2/788 (0.3)
	> 1.5 x ULN	0/418	1/422 (0.2)	0/412	0/774	4/788 (0.5)

Only parameters for which patients that had at least 1 PCS postbaseline value (high or low) are included.

No patients had non-PCS baseline and PCS postbaseline values for the following: basophil count, mean corpuscular hemoglobin, mean corpuscular volume (high), and monocyte count

LLN = lower limit of normal; N = number of patients with non-PCS baseline values and at least 1 nonmissing postbaseline value; n = number of patients with non-PCS baseline values and at least 1 PCS postbaseline value; PCS = potentially clinically significant; ULN = upper limit of normal.

Long Term Safety Trials

The parameters that were reported as PCS in at least 2% of all CIC or all IBS-C patients were: low hemoglobin (2.5% of CIC patients and 1.3% of IBS-C patients), low lymphocytes (3.8% of CIC patients and 2.4% of IBS-C patients), and low neutrophils (2.2% of CIC patients and 2.0% of IBS-C patients). See Table 78.

There were no meaningful differences in the AE profiles between the patient groups.

The most frequently reported hematology TEAEs in the Phase 3 open-label LTS studies were anemia (0.7%), hemoglobin decreased (0.2%), and white blood cell count increased (0.2%). Two events were reported as SAEs: a CIC patient with aplastic anemia (0563006; see Appendix IV for an in-depth discussion of this case) and 1 IBS-C patient with anemia (0733119). A total of 9 patients discontinued from the Phase 3 open-label LTS studies as the result of a hematology-related TEAE. These included 5 IBS-C patients with anemia (0253134, 0353112, 0362041, 0622011, and 0733119); a CIC patient with aplastic anemia (0563006); 1 IBS-C patient with neutrophil count decreased and white blood cell count decreased (1303110); 1 IBS-C patient with lymphocyte count decreased, neutrophil count decreased, and white blood cell count decreased (0852015); and 1 IBS-C patient with platelet count decreased (0982014).

Table 78: Incidence of Potentially Clinically Significant Hematology Parameters During the Phase 3 Open-Label Long-Term Safety Studies (Group 3)—Safety Population

Hematology Parameter	PCS Criteria	CIC Patients (N = 1129)	IBS-C Patients (N = 2146)
		n/N1 (%)	n/N1 (%)
Hematocrit	< 0.9 x LLN	13/1082 (1.2)	8/2071 (0.4)
	> 1.1 x ULN	2/1082 (0.2)	3/2071 (0.1)
Hemoglobin	< 0.9 x LLN	27/1079 (2.5)	27/2059 (1.3)
Lymphocytes	< 0.8 x LLN	41/1073 (3.8)	50/2058 (2.4)
	> 1.5 x ULN	0/1073	4/2058 (0.2)
Mean corpuscular volume	< 0.9 x LLN	1/1082 (0.1)	0/2076
	> 1.1 x ULN	2/1082 (0.2)	0/2076
Monocytes	> 3 x ULN	1/1087 (0.1)	3/2086 (0.1)
Neutrophils	< 0.8 x LLN	24/1074 (2.2)	41/2067 (2.0)
	> 1.5 x ULN	14/1074 (1.3)	14/2067 (0.7)
Platelets	< 0.5 x LLN	1/1081 (0.1)	1/2079 (0.0)
	> 1.5 x ULN	3/1081 (0.3)	7/2079 (0.3)
Red blood cells	< 0.9 x LLN	13/1084 (1.2)	7/2080 (0.3)
	> 1.1 x ULN	3/1084 (0.3)	1/2080 (0.0)
White blood cells	< 0.7 x LLN	7/1086 (0.6)	5/2086 (0.2)
	> 1.5 x ULN	4/1086 (0.4)	5/2086 (0.2)

No patients had non-PCS baseline and PCS postbaseline values for the following: basophils, eosinophils, and hemoglobin (high), and mean corpuscular hemoglobin.

LLN = lower limit of normal; N1 = number of patients with non-PCS baseline values and at least 1 nonmissing postbaseline value during the open-label period; n = number of patients with non-PCS baseline values and at least 1 PCS postbaseline value during the open-label period; PCS = potentially clinically significant; ULN = upper limit of normal.

Blood Chemistries

Phase 3 Controlled Trials

With the exception of bicarbonate, there were no notable shifts in chemistry parameters at any time during treatment, including the end of treatment. In the CIC patients, 1.7% of the patients treated with linaclotide 290 ug and 1.4% of the patients treated with linaclotide 145 ug had a shift in bicarbonate from normal at baseline to low during the Treatment Period vs. 0.7% for placebo.

In the IBS-C patients, 5.0% of linaclotide patients had a shift in bicarbonate from normal at baseline to low at least once during the Treatment Period vs. 2.5% for placebo. In most of these patients, the decreased bicarbonate value was 19 mmol/L (just below the lower limit of normal, 20 mmol/L), occurred on a single occasion, returned to the normal range by the end of the Treatment Period, and was not associated with any particular TEAE. At the end of the Treatment Period, 2.7% of linaclotide patients had a shift in bicarbonate from normal at baseline to low vs. 1.3% for placebo. In most of these patients, the low bicarbonate at the end of the Treatment Period was in the 18 to 19 mmol/L range, was the first occurrence of a low value, and represented a value that was similar to a baseline value (e.g., the patient had a bicarbonate value at screening or baseline that was 20 mmol/L).

The incidence of PCS (potentially clinically significant) chemistry values was generally low and similar across treatment groups (< 2% for each parameter).

In the CIC trials, one patient (0090109) treated with placebo and one patient (1030114) treated with linaclotide 290 ug had PCS low bicarbonate values. In both patients, the PCS value was transient and was not associated with diarrhea. In IBS-C trials, there were a greater number of patients who had PCS low bicarbonate values (0.6% with linaclotide vs 0% with placebo). One (0462014) of these 5 patients had a PCS value on Day 138 and also at the end of the Treatment Period concurrent with diarrhea. In the remaining 4 patients, the PCS value was transient and was not associated with diarrhea.

No notable differences were observed across the treatment groups, and no chemistry-related TEAEs (preferred term) were reported in $\geq 1\%$ of either CIC or IBS-C patients treated with linaclotide. None of the events were reported as SAEs. Three linaclotide CIC patients discontinued from the study because of abnormal chemistry results: hyponatremia (patient 0060102 who did not report diarrhea as an AE); blood glucose increased (patient 0223004); and hypothyroidism and hepatic enzyme increased (patient 0310125). Two placebo IBS-C patients discontinued from the study because of abnormal chemistry results (alanine aminotransferase increased in 1 patient and aspartate aminotransferase increased in the other patient)

Long Term Safety Trials

The incidences of PCS chemistry values were generally low. The parameters that were reported as PCS in at least 2% of all CIC or all IBS-C patients were: low glucose (2.7% of IBS-C patients and 1.8% of CIC patients), high glucose (2.0% of CIC patients and 1.3% of IBS-C patients), and high uric acid (4.0% of IBS-C patients and 0 CIC patients). See Table 79.

The most frequently reported chemistry-related TEAEs in the Phase 3 open-label LTS studies were aspartate aminotransferase increased (0.9%), alanine aminotransferase increased (0.8%), hypokalemia (0.7%), and hypercholesterolemia (0.5%). None of the events were reported as SAEs. A total of 7 patients discontinued from the Phase 3 open-label LTS studies as the result of a chemistry-related TEAE. These included 2 CIC patients (0690116 and 0950106) and 1 IBS-C patient (1073102) who had ADOs of hepatic enzyme increased; 1 IBS-C patient (1202018) who had ADOs of alanine and aspartate aminotransferase increased; 1 CIC patient (0640114) who had an ADO of blood bilirubin increased; 1 IBS-C patient (0443136) who had ADOs of blood glucose increased and glucose urine present; and 1 CIC patient (0403008) who had an ADO of hyperglycemia. No reported cases meeting criteria for Hy's law.

Table 79: Incidence of Potentially Clinically Significant Chemistry Parameters During the Phase 3 Open-Label Long-Term Safety Studies (Group 3)—Safety Population

Laboratory Parameter	PCS Criteria	CIC Patients (N = 1129)	IBS-C Patients (N = 2146)
		n/N1 (%)	n/N1 (%)
Alanine aminotransferase	≥ 3 x ULN	6/1089 (0.6)	11/2084 (0.5)
Albumin	< 0.9 x LLN	1/1088 (0.1)	1/2085 (0.0)
	> 1.1 x ULN	2/1088 (0.2)	0/2085
Aspartate aminotransferase	≥ 3 x ULN	10/1090 (0.9)	9/2084 (0.4)
Bicarbonate	< 0.9 x LLN	10/1089 (0.9)	28/2082 (1.3)
Bilirubin, total	> 1.5 x ULN	4/1087 (0.4)	10/2079 (0.5)
Blood urea nitrogen	> 1.2 x ULN	16/1089 (1.5)	22/2078 (1.1)
Chloride	< 0.9 x LLN	0/1090	2/2087 (0.1)
Cholesterol	> 1.6 x ULN	6/1084 (0.6)	10/2080 (0.5)
Creatinine	> 1.3 x ULN	11/1088 (0.6)	7/2080 (0.3)
Glucose, nonfasting	< 0.8 x LLN	19/1075 (1.8)	55/2060 (2.7)
	> 1.4 x ULN	22/1075 (2.0)	27/2060 (1.3)
Magnesium	< 0.9 x LLN	5/1089 (0.5)	7/2083 (0.3)
	> 1.1 x ULN	1/1089 (0.1)	2/2083 (0.1)
Phosphorus	< 0.9 x LLN	21/1086 (1.9)	30/2077 (1.4)
	> 1.1 x ULN	9/1086 (0.8)	14/2077 (0.7)
Potassium	< 0.9 x LLN	19/1077 (1.8)	32/2063 (1.6)
	> 1.1 x ULN	5/1077 (0.5)	24/2063 (1.2)
Protein, total	< 0.9 x LLN	1/1087 (0.1)	0/2086
	> 1.1 x ULN	2/1087 (0.2)	8/2086 (0.4)
Sodium	< 0.9 x LLN	0/1090	0/2087
	> 1.1 x ULN	1/1090 (0.1)	0/2087
Uric acid ^a	< 0.9 x LLN	0/6	8/1938 (0.4)
	> 1.1 x ULN	0/6	77/1938 (4.0)

No patients had non-PCS baseline and PCS post baseline values for the following: alkaline phosphatase, bicarbonate (high), calcium, chloride (high), and sodium (low).

a Uric acid analysis was not implemented in the Phase 3 CIC trials and was implemented late in the course of the LTS studies; only 6 CIC patients had a baseline value in the LTS study.

LLN = lower limit of normal; N1 = number of patients with non-PCS baseline values and at least 1 nonmissing post baseline value during the open-label period; n = number of patients with non-PCS baseline values and at least 1 PCS post baseline value during the open-label period; PCS = potentially clinically significant; RI = randomization ineligible patients from trials LIN-MD-01 and MCP-103-303 for the CIC indication, or trials LIN-MD-31 and MCP-103-302 for the IBS-C indication; RO = rollover patients who completed any of the Phase 2 or Phase 3 double-blind studies; ULN = upper limit of normal.

Urinalysis

Phase 3 Controlled Trials

There were no clinically meaningful differences between the placebo and linaclotide treatment groups for the urinalysis parameters analyzed, and the changes from baseline were inconsequential. There were no differences between placebo and linaclotide patients in the incidence of urinalysis-related TEAEs and none of these TEAEs were reported as SAEs or ADOs.

Long Term Safety Trials

There were no clinically meaningful mean changes from baseline in either CIC or IBS-C patients for any of the parameters analyzed. The most frequently reported urinalysis-related TEAEs in the Phase 3 open-label LTS studies were blood urine present, hematuria, and white blood cells urine positive (all at 0.4%). None of the events listed was reported as an SAE. Two IBS-C patients discontinued from the study due to a urinalysis-related TEAE: glucose urine present (0443136) and proteinuria (0643114).

7.4.3 Vital Signs

Phase 3 Controlled Trials (Group 1)

There were no clinically meaningful changes in vital sign values or meaningful differences among the treatment groups. With the exception of weight, no vital sign parameter was reported as PCS in $\geq 2\%$ of patients in any treatment group; the PCS changes in weight were similar between treatment groups in both weight loss and weight gain.

The incidence of TEAEs was low and similar between linaclotide- and placebo-treated patients for each indication and preferred term. There were 3 CIC patients (all in LIN-MD-01) who had orthostatic hypotension reported as TEAEs. One of these patients (0570150) who was treated with 290 ug/day had PCS low SBP and DBP values, with an associated SAE of orthostatic hypotension (see Section 8.7 for link to narrative); at the time of the event, the patient was dehydrated as a result of nausea, vomiting, and diarrhea. The second patient (0140103) had orthostatic hypotension that occurred concurrently with reduced fluid intake, nasopharyngitis, and bronchitis (reported as an SAE). The third patient (0600103) experienced orthostatic hypotension on day 15 with no concurrent AEs. In the IBS-C Safety Population there were 2 placebo patients in trial MCP-103-302 who had PCS increase in DBP and related TEAEs of hypertension (0632035) and blood pressure diastolic increased (0632050).

Long-Term Safety Trials

There were no clinically meaningful changes in vital sign values over time. With the exception of weight, no vital sign parameter was reported as PCS in $\geq 2\%$ of patients in any patient population. PCS weight decreases occurred in 10.6% of CIC and 9.4% of

IBS-C patients; PCS weight increases occurred in 13.4% of CIC and 7.6% of IBS-C patients.

The only TEAE reported in $\geq 1\%$ of all patients was hypertension (1.5%). There were 2 CIC patients (0103035 and 1103005) and 3 IBS-C patients (0032010, 0453106, and 0872007) who had PCS elevations in blood pressure that were reported as TEAEs of hypertension or blood pressure increased. One CIC patient (018002) had an SAE of bradycardia and 1 CIC patient (0720108) had an SAE of hypertension. One CIC patient (1062006) had an event of hypertensive crisis and an SAE of pneumonia. One CIC patient (0033016) had a PCS decrease in pulse and an associated TEAE of bradycardia.

7.4.4 Electrocardiograms (ECGs)

Medical Officers Comments:

The Applicant was waived performing a TQT study secondary to the low systemic exposure with this drug. However, ECG's were performed in a subset of the phase 3 trials and there were no clinically meaningful changes in ECG parameters among the treatment groups.

ECGs were obtained at the Screening Visit and End of Treatment Visit on all patients during the phase 3 double-blind, placebo-controlled trials, and at the end of the RW Period in MCP-103-303 and LIN-MD-31. In addition, a "triplicate ECG" program was conducted at the request of the FDA. A total of 424 CIC patients (134 placebo and 290 linaclotide) and 326 IBS-C patients (164 placebo and 162 linaclotide) in the Phase 3 placebo-controlled trials participated in the triplicate ECG program to determine if linaclotide had effects on the QT/QTc interval.

Phase 3 Controlled Trials (Group 1)

Overall, there were no clinically meaningful changes in ECG parameters among the treatment groups. See Table 80.

There were 3 CIC patients who had shifts to clinically significant ECGs at the end of the trial.

- Patient 0880132 (LIN-MD-01, placebo): at the end of treatment the investigator reported a TEAE of a clinically significant ECG finding (first-degree atrioventricular (AV) block). Although the first degree AV block was not noted at the Screening Visit, the PR interval was 204 msec at the Screening Visit and 208msec at end of treatment
- Patient 0663003 (MCP-103-303, linaclotide 145 ug): at the end of treatment, this patient's ECG showed first-degree AV block that was not present at the Screening Visit and that occurred in association with an SAE of chest pain. The PR interval was 185 msec at screening and increased to 211msec at the end of

treatment. At the end of the RW Period, the PR interval returned to a value of 187msec, while the patient continued to be treated with linaclotide.

- Patient 0283003 (MCP-103-303, linaclotide 145 ug): after 11 days of treatment, this patient had an ECG finding of atrial fibrillation that was not present at the Screening Visit (when the patient was observed to be in normal sinus rhythm). The atrial fibrillation, which was associated with a controlled rate of 76 beats/minute, was reported as an SAE and resulted in the patient being withdrawn from the study.

There were 2 IBS-C patients who had shifts to clinically significant ECGs at the end of the trial:

- Patient 0122021 (MCP-103-302, placebo): at the end of trial, this patient had an ECG finding of a right ventricular conduction delay that was not noted at the Screening Visit. The QRS interval was 89msec at the Screening Visit and 88msec at the end of the trial.
- Patient 0882024 (MCP-103-302, linaclotide 290 ug): at the Week 12 Visit, the patient had an ECG that showed sinus tachycardia (heart rate 134 beats/minute) with ventricular premature complexes; the HR at the Screening Visit was 121 beats/minute, but ventricular premature complexes were not noted. The ECG at the Week 16 Visit was unchanged from the Week 12 Visit; the patient was withdrawn from the study, and the sinus tachycardia was recorded as an AE.

There were 16 CIC patients (10 linaclotide and 6 placebo), and 9 IBS-C patients (2 linaclotide and 7 placebo) who had a postbaseline PCS value for at least 1 ECG parameter. Five of the patients had PCS high QTc intervals (i.e., > 500msec): 3 treated with placebo and 2 treated with linaclotide. Eight of the patients had PCS QTc interval changes \geq 60msec: 3 treated with placebo and 5 treated with linaclotide. Some of these patients are in the triplicate ECG cohort.

None of the patients who had PCS ECG values had TEAEs that were associated with these PCS values.

Long-Term Safety Studies (Group 3)

Single 12-lead ECGs were performed at baseline and at visits V3 (day 43), V7 (Week 52), and V9 (Week 78) in LIN-MD-02 and MCP-103-305. Measurements Overall, there were no clinically meaningful changes in ECG parameters or differences between the patient populations were recorded for heart rate, PR interval, QRS interval, RR interval, and QT interval.

One CIC patient (0880139) who had a PCS PR interval (276 msec) had an associated TEAE of extrasystoles.

Table 80: Incidence of Postbaseline Potentially Clinically Significant ECG Parameters During the Treatment Period of Phase 3 Placebo-Controlled CIC and IBS-C Trials (Group 1)—Safety Populations

ECG Parameter (msec)	CIC			IBS-C Patients	
	Placebo	Linaclotide		Placebo	Linaclotide
	(N = 423)	145 ug (N = 430)	290 ug (N = 422)	(N = 798)	290 ug (N = 807)
	n/N1 (%)	n/N1 (%)	n/N1 (%)	n/N1 (%)	n/N1 (%)
QRS ≥ 150	4/415 (1.0)	2/413 (0.5)	0/405	3/747 (0.4)	0/758
PR ≥ 250	2/414 (0.5)	1/413 (0.2)	2/404 (0.5)	2/749 (0.3)	0/758
QTcB					
> 500	0/416	2/414 (0.5)	0/406	2/750 (0.3)	0/759
Change ≥ 60	1/416 (0.2)	0/414	1/406 (0.2)	2/750 (0.3)	2/759 (0.3)
QTcF					
> 500	1/416 (0.2)	0/414	0/406	0/750	0/760
Change ≥ 60	0/416	1/414 (0.2)	2/406 (0.5)	1/750 (0.1)	1/760 (0.1)

CIC Trials: LIN-MD-01 and MCP-103-303; IBS-C Trials: LIN-MD-31 and MCP-103-302.

N1 = number of patients with non-PCS baseline values and at least 1 nonmissing postbaseline value; n = number of patients with non-PCS baseline values and at least 1 PCS postbaseline value; PCS = potentially clinically significant; QTcB = QTc Bazett; QTcF = QTc Fridericia.

7.4.5 Special Safety Studies/Clinical Trials

None

7.4.6 Immunogenicity

Medical Officer's Comments:

The Applicant did not perform immunogenicity testing on LINZESS during clinical development. The rationale they provided for this decision is provided below. An IR was sent to the applicant to analyze the reported AE's on the Preferred Terms of immune system disorders - hypersensitivity, drug hypersensitivity, anaphylactic reaction and skin and subcutaneous tissue disorders – urticaria. The applicant completed a thorough analysis, which is presented below. Review of these data and analyses show no safety signals for an association with hypersensitivity.

Final consult review from the Division of OBP pending as of 4/12/12. However, verbal communication with Susan Kirshner, PhD indicates she plans to recommend a PMC to address possible reaction to chronic use of IgA antibody production, which may effect efficacy.

Applicant's Rational for not Performing Immunogenicity Testing

LINZESS is a small (14 amino acid) orally administered peptide. Orally administered LINZESS is minimally absorbed into the systemic circulation, and is reduced and

proteolyzed in the intestine. Therefore, any potential for an immune response to LINZESS would likely be limited to the intestinal mucosa. In general, the intestinal mucosal immune system (e.g. gut-associated lymphoid tissue) acts primarily to suppress immune responses to the enormous quantities of antigens in ingested foods. An orally administered peptide would therefore not be expected to produce a robust immune response as might a parenterally administered protein. In general, peptides with molecular weights < 10,000 daltons are usually not immunogenic even when administered parenterally. Orally administered LINZESS has a molecular weight of 1526 daltons.^{13,14}

Applicants Reply to IR and Analysis of Hypersensitivity

A search of the database from the phase 2 and 3 clinical studies (including all phase 2 and 3 placebo-controlled efficacy studies, as well as the long-term safety [LTS] Studies) revealed that there were 52 patients who had Preferred Terms (PTs) related to hypersensitivity. The lower level term (LLT) provides an adequate explanation for the PTs related to hypersensitivity for 24 of the 52 patients. In 14 of the 15 patients with the PT, “drug hypersensitivity,” the LLT describes a reaction to a specific drug, other than study drug. Likewise, the PT, “hypersensitivity,” is explained by the LLT in 9 of the 13 patients with that particular PT. In each of the 9 cases, the cause of the hypersensitivity is related to environmental allergies (i.e., hay fever, or seasonal allergic rhinitis) or a worsening of environmental allergies. Only one of the 23 patients with the PT, “urticaria,” has an LLT that explains the occurrence of the urticaria. Pt 0072015 had urticaria that is explained by the LLT, “hives related to Flexeril.” Therefore, a total of 28 pts had PTs related to hypersensitivity where the LLT provided no explanation for the occurrence of the PT.

Controlled Trials

Ten patients had PTs related to hypersensitivity during a phase 2 or 3 placebo-controlled trials:

- 1 during the Pretreatment Period (patient was later randomized to placebo)
- 7 during the Treatment Period or within 1 day of treatment ending (5 on linaclotide, 2 on placebo)
- 1 more than 1 day after treatment ended (placebo)
- 1 during the RW Period of a Phase 3 trial (linaclotide during the RW Period, placebo during the Treatment Period)

For the PT, urticaria, 3 linaclotide-treated patients and 1 placebo-treated patient reported the AE during the Treatment Period. During the RW Period, an additional linaclotide-treated patient reported urticaria. The likelihood that linaclotide caused the urticaria in the 4 linaclotide-treated patients is low given that the urticaria resolved and did not recur while the patient continued to take linaclotide.

For the PT terms, hypersensitivity and drug hypersensitivity the number of linaclotide-treated patients (2 patients) who reported either of the two AEs during the Treatment Period was very similar to the number of placebo-treated patients (1 patient) who reported either of the two terms. Likewise, the number of patients who withdrew from a study for either PT was the same (1 patient) in each treatment group.

When the PT terms, hypersensitivity, drug hypersensitivity, and urticaria, are considered together, 6 linaclotide-treated patients reported one of the PTs during the Treatment Period or RW Period versus 2 placebo-treated patients. However, the urticaria resolved in 4 of the linaclotide-treated patients and did not recur despite continuation of linaclotide treatment leaving 2 linaclotide-treated and 2 placebo-treated patients for whom the AE may have been ascribed to study drug (during blinded treatment). See Table 81.

Table 81: Patients with Preferred Terms (Drug Hypersensitivity, Hypersensitivity, and Urticaria) for which the Lower Level Term Does Not Provide an Adequate Explanation for the Preferred Term: All Phase 2 and 3 Placebo-controlled Studies

<i>Pt ID #</i>	<i>AE Preferred Term</i>	<i>Lower Level Term^b</i>	<i>Treatment</i>	<i>ADO?</i>	<i>Start Day</i>	<i>Stop Day</i>	<i>Days on Treatment</i>
AEs During the Pretreatment Period							
MCP-103-202.267013	Urticaria	Hives On Neck, Back And Face	Placebo	N	-20	-6	79
AEs during the Treatment Period (or within 1 day of Treatment Ending)							
MCP-103-004.08002	Hypersensitivity	Allergic Reaction	Linaclotide	Y	4	4	3
MCP-103-004.08004	Hypersensitivity	Allergic Reaction	Linaclotide	^c N	2	2	2
MCP-103-202.244010	Urticaria	Rash Urticaria R Arm	Linaclotide	N	11	13	78
0043001	Urticaria	Urticaria	Linaclotide	N	26	33	89
0063130	Urticaria	Urticaria, etiology Unknown	Placebo	N	2	5	86
0243107	Drug hypersensitivity	Allergic Reaction To Study Drug	Placebo	Y	1	1	1
0632030	Urticaria	Urticaria	Linaclotide	N	125	127	183
AEs Occurring after the Treatment Period (> 1 day after treatment ended)							
1192019	Urticaria	Hives	Placebo	N	89	91	87
AEs during the Randomized Withdrawal Period							
0323007 ^a	Urticaria	Hives	Linaclotide	N	91	111	113

Long Term Safety Trials

Eighteen patients had PTs related to hypersensitivity during the long-term safety trials where the LLT gave no adequate explanation. See Table 82.

- 1 patient (0690127) had an anaphylactic reaction on Day 277 that was not considered an SAE. This patient was a 62-year-old white female who had a medical history that is significant for hypertension, hypothyroidism, Type 2 diabetes mellitus, sleep apnea, and arthritis. The manifestations of the

anaphylactic reaction are not provided in the programmed narrative, but the event was treated with oral diphenhydramine (50 mg) and it resolved on the same day it started (Day 277). The AE did not require any interruption in linaclotide treatment, as the patient remained on therapy for 544 days. The investigator considered the AE to be mild and unrelated to treatment. The fact that the AE resolved without any interruption in linaclotide treatment and the lack of any recurrences with continued linaclotide treatment make it unlikely that the anaphylactic reaction was caused by linaclotide.

- 2 patients had hypersensitivity reactions, described as an allergic reaction in one (Pt 0373122) and as an “allergic reaction (hives) (itching)” in the other (Pt 0073012).
- 15 patients had urticaria.

Only 1 patient withdrew from the LTS Studies for a PT related to hypersensitivity (Pt 0083150; PT = urticaria; LLT = hives on face). It is unlikely that any of the PTs list are related to study drug because the events in 14 of the 18 patients resolved during treatment (and not as a result of linaclotide being withheld) and all but one of these patients continued treatment for more than 100 days without a recurrence of the event.

It is notable that 3 patients had urticaria with a stop day of “ongoing.” In each of these cases, the urticaria lasted for more than 6 weeks, which meets the definition of chronic urticaria. Two of these 3 patients have a potential alternative explanation for their urticaria. Patient 0610103 had a bee sting on the day that the urticaria started, and Patient 0493014 had a history of Raynaud’s disease, SLE, and Sjogren’s syndrome, all of which are associated with urticaria.

Table 82: Patients in the LTSS with Preferred Terms (Anaphylactic Reaction, Hypersensitivity, and Urticaria) where the Lower Level Term does Not Provide an Adequate Explanation for the Preferred Term

<i>Pt #</i>	<i>AE Preferred</i>	<i>Lower Level Term^b</i>	<i>ADO?</i>	<i>Start Day</i>	<i>Stop Day</i>	<i>Days on Treatment</i>
MCP-103-202.265003	Urticaria	Hives	N	524	545	547
0032002	Urticaria	Hives On Right Arm	N	302	303	477
0073012	Hypersensitivity	Allergic Reaction (Hives) (Itching)	N	12	13	554
0083139	Urticaria	Hives On Face	N	73	93	259
0083150	Urticaria	Hives	Y	25	29	26
0283104 ^a	Urticaria	Hives	N	188	ongoing	516
0283109	Urticaria	Hives	N	345	345	467
0352010	Urticaria	Urticaria	N	10	11	285
0493014	Urticaria	Hives	N	345	ongoing	546
0610103	Urticaria	Hives	N	505	ongoing	547
0690127	Anaphylactic reaction	Anaphylactic Reaction	N	277	277	544
0712001	Urticaria	Hives On Neck And	N	40	45	467
0872024	Urticaria	Hives	N	138	145	364
1252030	Urticaria	Urticaria	N	39	41	368
0043122	Urticaria	Generalized Upper Body	N	5	6	466
0373122	Hypersensitivity	Allergic Reaction	N	97	106	446
1123103	Urticaria	Hives	N	29	49	501
1202007	Urticaria	Hives	N	175	210	546

Abbreviations: AE: adverse event; ADO: adverse event associated with withdrawal from the study.

a Pt 0283104 reported urticaria on 3 occasions; D188-D202, D256-D266, D333 ongoing (in study 516 days).

b The LLT is a verbatim term, presented in the table exactly as it is entered into the electronic case report form.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Medical Officer's Comments:

There was increasing incidence of diarrhea and drops outs in the phase 2 dose ranging trials with increasing dose, especially noted in the high dose 574 µg group. See discussion in Section 6.1.8 on page 108.

The two doses tested in the phase 3 trials showed minimal difference in AE's (especially diarrhea), though there was a slight trend toward increased diarrhea in the higher dose in some of the trials, it was not consistent across trials.

Dose reduction from 290µg to 145µg was performed in 32% of the patients in the long term safety trials, approximately half of these patients then completed the trial and half required discontinuation of linaclotide. The far majority of the patients required dose suspension or reduction for the AE of diarrhea; this most commonly occurred in the first 3 weeks of the trial. See discussion in See Section 7.3.4 - Significant Adverse Events on page 148.

See discussion in Section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations – Review of Dose Ranging Trials on page 108.

MCP-103-303 [Phase 3 in CIC]: Safety Information

Patients experiencing at least 1 TEAE were somewhat higher in the linaclotide groups, with no dose-related trends (placebo - 50.2 %, linaclotide 145µg - 56.2 % and linaclotide 290µg - 54.8 %). Patients experiencing serious AEs were 2.4 % for placebo, 1.4 % for linaclotide 145µg and 1.8 % for linaclotide 290µg. Discontinuations due to TEAE were higher in the two linaclotide groups compared to placebo (3.8 % for placebo, 5.1 % linaclotide 145 µg and 5.1 % for linaclotide 290µg). However, there was no dose-related trend in discontinuation rates.

Diarrhea occurred at a greater (twice) frequency in the linaclotide (12.4% and 13.8%) groups compared to placebo (6.7%). The frequency of diarrhea was slightly higher in the 290µg dose group (13.8 %). Three patients (1.4%) in each linaclotide dose group had severe diarrhea, and 1 patient (0.5%) in the placebo group had severe diarrhea. Discontinuation rates for diarrhea were 0.5 %, 3.2 % and 2.8 % for placebo, 145 µg and 290µg doses respectively. In general, incidence of diarrhea, nausea, abdominal pain and headache were highest in the 290µg dose group, although the difference between the two groups was not marked for these AEs.

LIN-MD-01 [Phase 3 in CIC]: Safety Information

While overall AEs were higher in the linaclotide groups compared to placebo (60.8 % vs. 54 %), there was no trend for dose-response for overall TEAE frequency with increasing dose (54 %, 64.8 % and 56.6 % for placebo, low dose and high dose linaclotide respectively). Serious AEs (SAEs) were 1.9 %, 1.4 % and 3.4 % respectively, for these cohorts. The percent discontinuation due to AEs was 4.7 %, 9.9 % and 9.8 % in the placebo, low dose and high dose groups, respectively.

The incidence of diarrhea was markedly higher in the linaclotide group (17.2 %) compared to placebo (2.8 %). However again there was no dose-response trend for diarrhea (2.8 %, 19.7 % and 14.6 % for placebo, low dose and high dose linaclotide).

The percentage of patients whose diarrhea was reported as 'severe' were more frequent in the higher linaclotide dose group compared to placebo or lower dose [0 %, 0.9 % and 2.4 % with placebo, 145µg and 290µg doses]. The highest dose also had two instances of defecation urgency and flatulence that were coded as severe, compared to none in the placebo or lower linaclotide dose. Of the total patients who discontinued due to AEs, the percentage of patients who discontinued due to diarrhea did not demonstrate dose-related trend (0.5 %, 5.6 % and 4.9 % in the placebo, low dose and high dose respectively). Abdominal pain [5.3 % vs. 2.3 % in placebo] and nausea [4.1 % vs. 3.3 %] also were more frequent in the linaclotide group but no distinct dose response trends were noted.

MCP-103-201 [Phase 2b in CIC]: Safety Information

Treatment-emergent adverse events (TEAEs) were reported by 31.9%, 35.6%, 32.1%, 29%, and 38.1% of patients in the placebo, 75, 150, 300 and 600µg groups, respectively. TEAEs leading to discontinuation were noted in 2.9%, 0%, 3.6%, 3.2%, and 4.8% of patients receiving the placebo, 75, 150, 300 and 600µg doses.

Incidence of diarrhea varied with linaclotide dose with the lowest incidence (4.8%) occurring in the 300µg dose group and the highest incidence (14.3%) occurring in the 600µg dose group. Dizziness was not reported in any patient who experienced diarrhea as a TEAE. 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 75, 150, 300 and 600µg doses, respectively).

Safety conclusions (phase 2b in IBS-C):

See also Section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations – Review of Dose Ranging Trials on page 108.

The 600µg exhibited the highest incidence of total and specific AEs, including discontinuation due to AEs. The % diarrhea, headache Dose Adjustments in the Long-Term Safety Trials and abdominal pain were seen more frequently at the 300µg dose compared to lower doses.

7.5.2 Time Dependency for Adverse Events

Medical Officer's Comments:

Overall the incidence of AE reporting decreased with time, being greater in the first four weeks. Diarrhea incidence also decreased with time.

Group 1 Phase 3 Controlled Trials – Pooled CIC and IBS-C Patients

The reporting of TEAEs, particularly diarrhea, tended to decrease over time in all treatment groups. See Table 84, on page 198.

Group 4S – All Linaclotide Patients

The commonly reported GI events were experienced within the first 3 months of treatment and declined successively with each 3-month interval. Most notably the incidence of diarrhea decreased from 27.7% during the first 3 months to 1.5% after Month 12. This probably was mostly secondary to dose reduction, and discontinuations for diarrhea. See Table 83.

Table 83: Treatment-Emergent Adverse Events Reported in ≥ 5% of CIC Patients in the Phase 3 Placebo-Controlled or Open-Label Long-Term Safety Studies (Group 4S) by Time of Onset— Safety Population

Adverse Event (Preferred Term)	Up to 3 months	> 3 to ≤ 6 months	> 6 to ≤ 9 months	> 9 to ≤ 12 months	> 12 months
	N = 1424	N = 1068	N = 904	N = 813	N = 731
Any TEAE	853 (59.9)	403 (37.7)	269 (29.8)	235 (28.9)	292 (39.9)
Diarrhea	326 (22.9)	115 (10.8)	39 (4.3)	20 (2.5)	27 (3.7)
Flatulence	80 (5.6)	17 (1.6)	7 (0.8)	3 (0.4)	2 (0.3)
Nausea	49 (3.4)	19 (1.8)	12 (1.3)	8 (1.0)	12 (1.6)
Abdominal pain	59 (4.1)	20 (1.9)	6 (0.7)	6 (0.7)	4 (0.5)
Sinusitis	35 (2.5)	16 (1.5)	21 (2.3)	18 (2.2)	17 (2.3)
Urinary tract infection	37 (2.6)	18 (1.7)	14 (1.5)	20 (2.5)	20 (2.7)
Upper respiratory tract infection	46 (3.2)	18 (1.7)	10 (1.1)	9 (1.1)	12 (1.6)
Headache	53 (3.7)	18 (1.7)	7 (0.8)	8 (1.0)	6 (0.8)
Abdominal distension	52 (3.7)	17 (1.6)	3 (0.3)	7 (0.9)	1 (0.1)

Table 84: Treatment-Emergent Adverse Events Reported in ≥ 2% of All Linacotide Patients in the Phase 3 Placebo-Controlled Trials (Group 1) and at an Incidence Greater Than Placebo by Time of Onset—Safety Population

Adverse Event (Preferred Term)	Number (%) of Patients											
	Placebo			Linacotide								
				145 ug/day			290 ug/day			Linacotide Total		
	≤ 4 wks N = 1218	4-12 wks ^a N = 1140	> 12 wks N = 812	≤ 4 wks N = 430	4-12 wks ^a N = 403	> 12 wks N = 224	≤ 4 wks N = 1227	4-12 wks ^a N = 1130	> 12 wks N = 783	≤ 4 wks N = 1657	4-12 wks ^a N = 1533	> 12 wks N = 1007
	n (%)			n			n (%)			n (%)		
Any TEAE	371 (30.5)	383 (33.6)	166 (20.4)	186	140	14 (6.3)	468	388	170	654	528	184
Diarrhea	25 (2.1)	11 (1.0)	8 (1.0)	56	17 (4.2)	1 (0.4)	166	55 (4.9)	12 (1.5)	222	72 (4.7)	13 (1.3)
Flatulence	30 (2.5)	5 (0.4)	3 (0.4)	22 (5.1)	3 (0.7)	0	43 (3.5)	12 (1.1)	2 (0.3)	65 (3.9)	15 (1.0)	2 (0.2)
Abdominal pain	22 (1.8)	16 (1.4)	3 (0.4)	8 (1.9)	9 (2.2)	0	40 (3.3)	19 (1.7)	4 (0.5)	48 (2.9)	28 (1.8)	4 (0.4)
Headache	33 (2.7)	11 (1.0)	3 (0.4)	13 (3.0)	3 (0.7)	0	39 (3.2)	12 (1.1)	0	52 (3.1)	15 (1.0)	0
Abdominal distension	12 (1.0)	5 (0.4)	3 (0.4)	11 (2.6)	4 (1.0)	0	22 (1.8)	9 (0.8)	4 (0.5)	33 (2.0)	13 (0.8)	4 (0.4)

wks = weeks.

a - 4-12 wks is defined as >4 weeks and ≤ 12 weeks.

7.5.3 Drug-Demographic Interactions

Medical Officer's Comments:

Drug-Demographic data is analyzed by the applicant for the phase 3 placebo-controlled trials only. In general, increased age (>65y) increased the incidence of AE's of diarrhea, by approximately 5%. There was also increased diarrhea in the male CIC population but not the male IBS-C population. Diarrhea AE's occurred more frequently in linaclotide treated Caucasian patients (17.1%), than in linaclotide treated Black patients (7.6%).

Phase 3 Controlled Trials – Group 1

Age

Overall, 1120 (87.8%) CIC patients and 1520 (94.7%) IBS-C patients in the Phase 3 placebo-controlled trials were < 65 years of age; and 155 (12.2%) CIC patients and 85 (5.3%) IBS-C patients were ≥ 65 year of age. A total of 50 (1.7%) patients (30 CIC and 20 IBS-C) were 75 years of age or older. The ≥ 65 year linaclotide patients comprised a higher percentage of males (29.6% vs. 8.1% for the younger linaclotide patients), a lower percentage of Blacks (13.4% vs. 20.7% for the younger linaclotide patients), and a lower percentage of Hispanics (5.6% vs. 12.0% for the younger linaclotide patients). Relative to their younger counterparts, older patients had higher incidences of hypertension, diabetes, and cardiovascular disorder histories.

With the exceptions of diarrhea and flatulence, there were minimal differences in the incidences of AEs based on age group or treatment. The incidence of diarrhea following linaclotide treatment was higher in the ≥ 65 years group (21.0%) than in the < 65 years group (14.4%); the placebo-treated patients who were ≥ 65 years also had a higher incidence of diarrhea than their younger counterparts (7.3% vs. 4.3%). Flatulence in linaclotide patients who were ≥ 65 years (11.0%) was greater than in placebo-treated patients (3.6%) but such a difference was not evident in the younger age group (4.5% linaclotide vs. 5.4% placebo).

As for CIC, the incidence of diarrhea was higher for both the linaclotide and placebo treatment groups in the ≥ 65 years group (23.8% and 7.0%, respectively), than in the < 65 years group (19.6% and 2.8%, respectively).

Potentially Significant Laboratory, Vital Sign, and ECG Values

There were no noteworthy differences between linaclotide and placebo patients in any of the PCS parameters assessed, in either indication.

Gender

The CIC patients from the phase 3 placebo-controlled trials comprised 142 (11.1%) male patients (46 placebo and 96 linaclotide) and 1133 (88.9%) female patients (377 placebo and 756 linaclotide). Similar percentages of male and female patients were included in the IBS-C Safety Population; 159 (9.9%) were male (89 placebo and 70 linaclotide) and 1446 (90.1%) were female (709 placebo and 737 linaclotide).

There were minimal treatment-related differences based on sex in the incidence of specific TEAEs in CIC patients. Overall, the AE incidence was lower in males than females (46.9% vs. 59.8%). There did appear to be a higher incidence of some AEs with the 290 ug dose compared to the 145 ug dose in male patients (e.g., diarrhea, flatulence, nausea); this effect was not seen in the female patients. The only AE for which there was a clear difference between placebo and linaclotide treatment in both male and female patients was diarrhea. The incidence of diarrhea in male patients who were treated with linaclotide was 15.6% compared with 6.5% in placebo patients, and the incidence in female patients who were treated with linaclotide was 15.1% compared with 4.5% in placebo patients.

In general, the AE incidence rates were somewhat lower in male patients than in female patients. In particular GI AEs appeared to be less frequent in male linaclotide patients than in female linaclotide patients. There was no difference in the overall AE incidence rates between the male placebo and male linaclotide patients. The incidence of diarrhea following linaclotide treatment was lower in male patients (15.7%) than in female patients (20.2%); however, the placebo-treated male patients had a higher incidence of diarrhea than their female counterparts (5.6% vs. 2.7%) resulting in lower absolute and relative differences between linaclotide and placebo rates of diarrhea in males compared to females.

There were no noteworthy differences between linaclotide and placebo patients in any of the PCS parameters assessed, in either indication.

Race

The CIC patients from the phase 3 placebo-controlled trials consisted of 972 (76.2%) Caucasians (327 placebo and 645 linaclotide), 273 (21.4%) Blacks (88 placebo and 185 linaclotide) and 30 (2.4%) patients of other races. Similar percentages of Caucasian and non-Caucasian patients were included in the IBS-C Safety Population [1243 (77.4%) Caucasians (612 placebo and 631 linaclotide), 301 (18.8%) Blacks (153 placebo and 148 linaclotide), and 61 (3.8%) other races (33 placebo and 28 linaclotide)]

For the CIC patients, there were minimal differences in the incidences of AEs between Caucasian and Black patients, with the exception of GI AEs, which were generally less frequent in linaclotide Black patients than in linaclotide Caucasian patients. The AE

incidence for the two doses was generally similar, and other than diarrhea, there was little difference between linaclotide-treated and placebo-treated Black patients. The incidence of diarrhea was 5.5% in placebo and 17.1% in linaclotide Caucasian patients; and 2.3% in placebo and 7.6% in linaclotide Black patients. The AE profile of the other non-Caucasian patients is not presented here because of the low numbers of patients. For IBS-C patients, there were minimal differences in the incidences of AEs between Caucasian and Black patients, with the exception of GI AEs, which were generally less frequent in linaclotide Black patients than in linaclotide Caucasian patients. As with CIC, the rate of diarrhea AEs was less in both linaclotide and placebo groups in the Black (0.7% in placebo and 10.1% in linaclotide) compared to the Caucasian (3.3% in placebo and 21.7% in linaclotide) subgroups. The AE profile of the other non-Caucasian patients is not presented here because of the low numbers of patients. Higher percentages of Black patients in each indication had PCS low neutrophil counts, but the differences between Caucasian and Black patients did not appear to be related to treatment. In the Black CIC patients 2.2% of the linaclotide group and 8.5% of the placebo group had PCS low neutrophils vs. 1.6% and 0.3% for the linaclotide and placebo groups in Caucasian CIC patients; in the Black IBS-C patients 4.3% of the linaclotide group and 3.4% of the placebo group had PCS low neutrophils vs. 1.8% and 0.3% for the linaclotide and placebo groups in Caucasian IBS-C patients.

Ethnicity

Phase 3 Controlled Trials – Group 1

The CIC Safety Population from the Phase 3 placebo-controlled trials included 127 (10.0%) Hispanic (36 placebo and 91 linaclotide) and 1148 (90.0%) non-Hispanic (387 placebo and 761 linaclotide) patients. Similar percentages of Hispanic and non-Hispanic patients were included in the IBS-C Safety Population [193 (12.0%) Hispanic (94 placebo and 99 linaclotide) and 1412 (88.0%) non-Hispanic (704 placebo and 708 linaclotide)]. Hispanic patients were somewhat younger than their non-Hispanic counterparts (mean age about 43 years vs 48 years in CIC patients and mean age about 40 vs. 44 years in IBS-C patients).

For the CIC patients, there were no apparent differences between linaclotide and placebo treatment based on ethnicity. The only TEAE for which there was a clear relationship to linaclotide treatment regardless of ethnic classification was diarrhea. The incidence of diarrhea in Hispanic patients who were treated with linaclotide [11.0% (vs 2.8% in placebo patients)] was slightly lower than the incidence in non-Hispanic patients who were treated with linaclotide [15.6% (vs 4.9% in placebo patients)]. Although the TEAE rates for GI events were similar for the 2 doses in non-Hispanic patients, the incidence of GI TEAEs was higher in the 290 ug dose than in the 145 ug dose in Hispanic patients.

For the IBS-C patients, the incidence of diarrhea in linaclotide Hispanic patients was lower than in the non-Hispanic patients (14.1% vs. 20.6%), but was higher in the

placebo Hispanic patients relative to the placebo non-Hispanic patients (4.2% vs. 2.8%). Hispanic patients who were treated with linaclotide also had a higher incidence of abdominal pain (8.1% vs. 1.1% on placebo).

There were no noteworthy differences between linaclotide and placebo patients in any of the PCS parameters assessed, for either indication.

Body Mass Index (BMI)

The CIC patients from the Phase 3 placebo-controlled trials comprised 890 (69.8%) patients with BMI < 30 kg/m² (279 placebo and 611 linaclotide) and 385 (30.2%) patients with BMI ≥ 30 kg/m² (144 placebo and 241 linaclotide) patients. Similar percentages of patients based on BMI category were included in the IBS-C Safety Population (1111 (69.2%) patients had a BMI < 30 kg/m² (559 placebo and 552 linaclotide), and 494 (30.8%) patients had a BMI ≥ 30 kg/m² (239 placebo and 255 linaclotide). The obese population had over twice the percentage of Black patients than the non-obese population (about 34% vs. 16% for CIC patients and about 29% vs. 13% for IBS-C patients).

For the CIC patients, the only AE for which there was a clear difference between placebo and linaclotide treatments, regardless of BMI classification, was diarrhea. The incidence of diarrhea in obese patients who were treated with linaclotide was 15.4% (vs. 2.1% in placebo patients) and the incidence of diarrhea in non-obese patients who were treated with linaclotide was 15.1% (vs. 6.1% in placebo patients). The incidence of AEs in both subgroups was comparable between the two linaclotide dose groups.

For the IBS-C patients, the incidence of AEs was similar across BMI subgroups. The incidence of GI AEs was higher in the linaclotide patients relative to the placebo patients in both BMI subgroups. Again, diarrhea was the most common AE; the incidence of diarrhea in obese IBS-C patients who were treated with linaclotide was 18.4%, compared with 2.1% in their placebo counterparts, and the incidence in non-obese IBS-C patients who were treated with linaclotide was 20.5% compared with 3.4% in their placebo counterparts.

There were no noteworthy differences between linaclotide and placebo patients in any of the PCS for Laboratory, Vital Sign, and ECG Values parameters assessed, for either indication.

7.5.4 Drug-Disease Interactions

Medical Officer's Comments:

Patients with hypertension and diabetes had a higher incidence of diarrhea as compared to patients without these concomitant diseases.

Patients with hypertension, diabetes, and cardiovascular disease may be more likely to experience clinical consequences of fluid shifts or electrolyte changes of any cause, including diarrhea, if they were to occur. The following sections present safety data on patients in the Phase 3 placebo-controlled studies who had these conditions based on baseline medical history.

Patients with Hypertension

In the phase 3 placebo-controlled trials there were 260 CIC patients and 277 IBS-C patients who had a preexisting condition of hypertension.

The diarrhea rate in the hypertensive IBS-C patients treated with linaclotide (25.2%) was higher than that observed in the Safety Population for all linaclotide IBS-C patients (15.1%; see Section 8.6.2.1.1). Flatulence incidence was also higher in the hypertensive IBS-C patients treated with linaclotide.

There were no notable differences in SAE's among the treatment groups. However, higher percentages of hypertensive linaclotide patients discontinued because of diarrhea than did placebo patients. These findings were consistent with the overall linaclotide Group 1 data.

Analyses of PCS laboratory data, PCS vital sign data, and PCS ECG data for hypertensive patients show that in the CIC patients treated with linaclotide, the parameters that were PCS at an incidence of $\geq 2\%$ were low lymphocyte count (3.1% vs. 2.2% for placebo), high glucose (3.1% vs. 2.2% for placebo), low potassium (2.5% vs. 2.3% for placebo), and decreased weight (2.4% vs. 1.1% for placebo). In the IBS-C patients treated with linaclotide, the parameters that were PCS at an incidence of $\geq 2\%$ were low lymphocyte count (2.2% vs. 0.8% for placebo), low hemoglobin (2.2% vs. 2.4% for placebo), high glucose (3.6% vs. 1.6% for placebo), low phosphorus (2.9% vs. 0 placebo patients), low potassium (6.8% vs. 3.2% for placebo), high uric acid (6.3% vs. 7.3% for placebo), and decreased weight (2.2% vs. 1.5% for placebo). There were no noteworthy differences between linaclotide and placebo patients in any of the other PCS parameters assessed, for either indication, and no noteworthy differences with the overall Group 1 data.

There was no evidence from the AEs reported to suggest any adverse consequences of fluid or electrolyte shift in hypertensive patients treated with linaclotide.

Patients with Diabetes

In the phase 3 placebo-controlled trials there were only 67 CIC patients and 67 IBS-C patients who had preexisting diabetes mellitus.

As was the case for all other subpopulations analyzed, the incidence of diarrhea was higher in the linaclotide-treated patients (8 of 45 CIC patients, and 10 of 38 IBS-C patients). Based on the PCS chemistry data, there is no evidence to suggest that diabetes patients treated with linaclotide are more susceptible to shifts in fluid or electrolytes. Overall, there did not appear to be any substantive differences in safety parameters between linaclotide-treated diabetic patients and the overall Safety Population treated with linaclotide.

Patients with Cardiovascular Disorders

In the Phase 3 placebo-controlled trials there were only 37 CIC patients and 9 IBS-C patients who had preexisting cardiovascular disorders.

Based on the PCS chemistry data, there is no evidence to suggest that patients with cardiovascular disorders who are treated with linaclotide are more susceptible to shifts in fluid or electrolytes. There did not appear to be any meaningful differences from the overall Safety Population.

7.5.5 Drug-Drug Interactions

Medical Officer's Comments:

No in vivo drug-drug interaction studies were performed. Linaclotide does not induce cytochrome P450 enzymes. Linaclotide also had no effect on the p-glycoprotein transporter mechanism.

Potential clinical interactions between linaclotide and drug classes commonly used by patients with CIC or IBS-C were explored by comparing the TEAE profiles in patients taking linaclotide or placebo in the Phase 3 placebo-controlled trials. Drug groupings used were diuretics, agents acting on the renin-angiotensin system, proton pump inhibitors, laxatives and mineral supplements, psychoanaleptics, selective serotonin reuptake inhibitors, and other antidepressants. These drugs were selected because they have the potential to make patients taking linaclotide more susceptible to diarrhea, electrolyte changes, and volume depletion.

In the CIC patients taking concomitant PPIs or laxatives, diarrhea occurred at higher rates in the total linaclotide and placebo groups compared with the respective Group 1 patients. In the IBS-C patients taking concomitant PPIs or laxatives, diarrhea occurred at similar rates in placebo patients but at higher rates in the linaclotide patients compared with the respective Group 1 patients. There were no notable differences in occurrence of other TEAEs or PCS laboratory values (in particular hypomagnesemia), between patients taking these concomitant medications and the Group 1 Safety Population. See Table 85.

In patients taking diuretics or agents affecting the renin-angiotensin system, the incidence of PCS changes in electrolytes was not meaningfully different between linaclotide or placebo patients in either indication.

Table 85: Incidence of Diarrhea in Patients Taking Proton Pump Inhibitors and Laxatives

Diarrhea	CIC Patients				IBS-C Patients	
	Placebo	Linaclotide			Placebo	Linaclotide 290 ug
		145 ug	290 ug	Total		
Group 1 n/N ^a (%)	20/42 3	69/430 (16.0)	60/422 (14.2)	129/85 2	24/79 8	160/807 (19.8)
PPI n/N1 (%)	6/61 (9.8)	16/57 (28.1)	10/67 (14.9)	26/124 (21.0)	2/129 (1.6)	32/12 1
Laxative n/N1 (%)	3/36 (8.3)	7/46 (15.2)	7/29 (24.1)	14/75 (18.7)	1/44 (2.3)	12/52 (23.1)

a. Safety Population

N = number of patients in Safety Population; N1 = number of patients in population taking the indicated concomitant medication; n = number of patients with diarrhea

7.6 Additional Safety Evaluations

Duplicate Patients

Medical Officer's Comments:

The applicant noted some patients had entered trials more than one time, which was not identified until after data lock occurred. Analysis shows no significant distortion to the data results from these patients.

Twenty-five patients participated in more than one trial or more than one time in the same trial.

The only notable difference in the TEAEs reported by these duplicate patients compared to all linaclotide treated patients (Group 4) is the relative infrequency of TEAEs of the GI disorders SOC (24% vs. 45.9%, respectively). The difference is attributable to the complete absence of TEAE Diarrhea in the duplicate-patient cases compared with the 30.8% incidence in all linaclotide-treated patients.

Two of the duplicate patients died. One death was a female patient (Case #6) who had enrolled in Phase 2 study MCP-103-202 (linaclotide 579 ug) and over a year later enrolled in Phase 3 trial LIN-MD-01 (linaclotide 145 ug); the cause of death was acute fentanyl toxicity due to application of multiple transdermal fentanyl patches. The second death was a male patient (Case #15) who enrolled in 2 LTS studies simultaneously (linaclotide 290 ug in both studies); the events leading to death were reported as severe anemia and metastatic lung cancer (in LIN-MD-02), and as esophageal squamous cell carcinoma stage IV (in MCP-103-305). Neither death was judged to be related to treatment. In addition to the 2 patients who died, there was one patient (Case #1), who experienced a non-fatal SAE of lymphoma (72 ug linaclotide in MCP-103-201 and 290 ug linaclotide in LIN-MD-01).

Apart from the 2 patients who died, there were no duplicate patients who discontinued from any study as a result of an AE.

Vital Signs, EKG's and PCS values are not significantly different in the duplicate patients from the Group 1 population.

7.6.1 Human Carcinogenicity

Unknown as this is a NME.

7.6.2 Human Reproduction and Pregnancy Data

Medical Officer's Comments:

No significant safety signals were noted in the patients who became pregnant during the trials. The pregnancy category should be category C, the labeling will need to be corrected.

Pregnant and lactating women were excluded from enrollment into any study in the linaclotide clinical development program. Throughout the linaclotide clinical development program, female study subjects of childbearing potential were required to have a negative serum pregnancy test upon enrollment. Sexually active women of childbearing potential were required to be on an effective method of birth control prior to and throughout the study. When pregnancy was reported and confirmed, the patient was taken off investigational product and the pregnancy followed through to outcome. As of 11-Oct-2010, a total of 24 cases were reported of women who became pregnant

while on investigational product in linaclotide trials. Of these, 5 were lost to follow-up and 5 have an expected date of delivery after 11-Oct-2010.

Two cases of ectopic pregnancy were reported in patients on investigational product. One patient had tubal ligation in the past, and the other was using an intrauterine device. The reliance on these birth-control methods would increase the risk of ectopic pregnancy. Five were terminated for non-medical reasons. Two of the women had a history of 1 or more elective pregnancy terminations. Two other women were very reluctant to report that they had an elective abortion, or even that they had been pregnant. The obstetric history of these last patients is not known. The other woman had an unremarkable obstetric history.

Data are available on 7 pregnancies that were followed to term. Of the 7 deliveries, 1 was by a pre-planned C-section and the other 6 were vaginal. All births were uncomplicated, and all babies were in good health.

Most of the pregnancies occurred in the open-label LTS studies. This finding is in line with the total patient exposure in these studies. Six women were noted to be pregnant in the phase 3 placebo-controlled trials, 2 in the linaclotide study arm and 4 in the placebo arm.

7.6.3 Pediatrics and Assessment of Effects on Growth

No trials in pediatric patients have been performed. Therefore, there is no data available on use in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Medical Officer's Comments:

There does not appear to be any significant abuse potential for linaclotide. There does not appear to be any withdrawal or rebound effect; however, patients rapidly return to baseline symptoms after drug withdrawal.

Single doses of linaclotide up to 2897 ug, which is about 10-fold the recommended therapeutic dose, were given to healthy volunteers with no consequences other than those associated with the pharmacological effects of linaclotide (i.e., diarrhea). Linaclotide was given to patients as per protocol, at doses up to 966 ug daily for 7 days. There were no known instances of intentional linaclotide overdose.

There are no known cases where linaclotide was used in a manner outside of the prescribed use as specified in the individual study protocols.

Withdrawal and Rebound

The Group 1 trials LIN-MD-31 and MCP-103-303 had 4-week Randomized Withdrawal Periods during which patients who were randomized to linaclotide (either 145 or 290 ug) during the Treatment Periods were re-randomized to either continue treatment with the same dose of linaclotide or receive placebo (i.e., linaclotide/linaclotide and linaclotide/placebo patients, respectively), and patients who were randomized to placebo during the Treatment Periods were allocated to treatment for 4 weeks with linaclotide 290 ug daily (i.e., placebo/linaclotide patients). There was no evidence in either study of a rebound effect (worsening of CIC or IBS-C symptoms relative to baseline after linaclotide was withdrawn). See analysis in Section 5.3.1.9 Other Endpoints, on page 64; and Section Other Endpoints, on page 85.

Patients did not experience new or previously unobserved types of AEs upon withdrawal of linaclotide treatment, suggesting that discontinuation of the drug did not lead to withdrawal effects. Patients who were treated with linaclotide during the Treatment Period and then received placebo in the RW Period had a decrease in the improvements in bowel and abdominal symptoms that were attained over the course of linaclotide treatment to a level similar to the placebo patients in the Treatment Period.

The incidence of RW Period AEs ($\geq 2\%$) for patients who received linaclotide in the Treatment Period and placebo in the 4-week RW period for CIC and IBS-C was analyzed. The corresponding AE rates for placebo patients in Group 1 over the first 4 weeks are presented as a comparator. Although the individual AE rates are slightly higher during the RW Period compared to the first 4 weeks of the Treatment Period, all rates are $< 4\%$ and do not represent a clinically meaningful increase in AEs for patients who received linaclotide followed by placebo. See Table 86 and Table 87.

Table 86: Randomized Withdrawal Period Treatment-Emergent Adverse Events Reported in ≥ 2% of Patients in Either the 145 ug-Placebo or 290 ug-Placebo Treatment Sequence in Study MCP-103-303 Compared With the First 4 Weeks of Treatment in Group 1 CIC Patients—Safety Population

Preferred Term	Number (%) of Patients		
	ISS CIC	MCP-103-303	
	Group 1 Placebo (first 4 weeks) (N = 423)	145 ug-Placebo (4-week RW Period) (N = 95)	290 ug-Placebo (4-week RW Period) (N = 86)
Any TEAE	145 (34.3)	18 (18.9)	15 (17.4)
Abdominal pain	7 (1.7)	2 (2.1)	3 (3.5)
Back pain	4 (0.9)	2 (2.1)	1 (1.2)
Nausea	11 (2.6)	3 (3.2)	0
Nasopharyngitis	9 (2.1)	0	2 (2.3)
Dizziness	1 (0.2)	2 (2.1)	0
Influenza	1 (0.2)	2 (2.1)	0

Table 87: Randomized Withdrawal Period Treatment-Emergent Adverse Events Reported in ≥ 2% of Patients in the 290 ug-Placebo Treatment Sequence in Study LIN-MD-31 Compared With the First 4 Weeks of Treatment in Group 1 IBS-C Patients—Safety Population

Preferred Term	Number (%) of Patients	
	ISS	LIN-MD-31
	Group 1 Placebo Patients (first 4 Weeks) (N = 798)	290 ug-Placebo (4-week RW Period) (N = 154)
Any TEAE	226 (28.3)	34 (22.1)
Sinusitis	10 (1.3)	4 (2.6)

There were no deaths reported during the RW Periods. Two patients in the MCP-103-303 trial had SAEs during the RW Period: atrial fibrillation in 1 patient and pulmonary embolism in the other patient. Both of these patients were receiving placebo at the time of the event. No SAEs were reported during the LIN-MD-31 RW Period.

Three patients had ADOs during the RW Period: 1 placebo/linaclotide patient, who experienced diarrhea and abdominal pain, and 1 linaclotide/placebo patient with fluid retention in the LIN-MD-31 trial; and 1 placebo/linaclotide patient in the MCP-103-303

trial had an ADO of severe abdominal discomfort, which was judged by the Investigator to be probably related to treatment. Overall, there were no clinically meaningful trends in the incidence of PCS laboratory, vital sign, or ECGs, and the results in the RW Period were consistent with the Treatment Period.

There were no meaningful differences between linaclotide and placebo patients in AEs related to the central nervous system, including lethargy, somnolence, and fatigue. There is no evidence to suggest that patients taking linaclotide would have altered physical or mental function that would affect driving or the ability to operate machinery.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

There is no postmarketing experience as Linaclotide is not marketed anywhere. Ironwood Pharmaceuticals and/or Forest Laboratories have not had any foreign marketing developments with the drug such as approval of marketing in any country or withdrawal or suspension of marketing in any country.

9 Appendices

9.1 Literature Review/References

See end of document

9.2 Labeling Recommendations

The labeling has been modified and is still in negotiation with the sponsor. Multiple changes were made in the labeling proposed by the sponsor. The current proposed labeling will carry a boxed warning with a contraindication in pediatric patients' up to age 6 and a warning to avoid use in pediatric patients' 6 through 16 years of age.

9.3 Advisory Committee Meeting

No AC meeting was held, because there are no significant safety or efficacy issues that required further discussion.

- ⁱ Zelnorm (tegaserod maleate) [package insert]. East Hanover, New Jersey; Novartis Pharmaceuticals Corporation: July 2006.
- ⁱⁱ Johanson JF, Drossman DA, Panas R, et al. Clinical trial: phase 2 study of lubiprostone for irritable bowel syndrome with constipation. *Aliment Pharmacol Ther* 2008;27:685–96.
- ⁱⁱⁱ Drossman DA, Chey W, Panas R, et al. Lubiprostone significantly improves symptom relief rates in adults with IBS. *Gastroenterology* 2007;132:2586–87.
- ⁴ American College of Gastroenterology Task Force on Irritable Bowel Syndrome. An evidence-based systematic review on the management of irritable bowel syndrome. *Am J Gastroenterol*. 2009;104(suppl 1):s1-s35.
- ⁵ Camilleri M, Andresen V. Current and novel therapeutic options for irritable bowel syndrome management. *Dig Liver Dis*. 2009;doi:10.1016/j.dld.2009.07.009.
- ⁶ Drossman, DA, Zhiming, L, Andruzzi, E, et al. US householders survey of functional gastrointestinal disorders: Prevalence, sociodemography, and health impact. *Dig Dis Sci* 1993; 38:1569.
- ⁷ Camilleri M, Andresen V. Current and novel therapeutic options for irritable bowel syndrome management. *Dig Liver Dis*. 2009;doi:10.1016/j.dld.2009.07.009.
- ⁸ Saito YA, Schoenfeld P, Locke GRI. The epidemiology of irritable bowel syndrome in North America: a systematic review. *Am J Gastroenterol* 2002;97:1910-5.
- ⁹ Hahn BA, Yan S, Strassels S. Impact of irritable bowel syndrome on quality of life and resource use in the United States and United Kingdom. *Digestion* 1999;60:77-81.
- ¹⁰ Dorn SD, Morris CB, Hu Y, et al. Irritable bowel syndrome subtypes defined by Rome II and Rome III criteria are similar. *J Clin Gastroenterol* 2009;43:214-20.
- ¹¹ Suh DC, Kahler KH, Choi IS, Shin H, Kralstein J, Shetzline M. Patients with irritable bowel syndrome or constipation have an increased risk for ischaemic colitis. *Aliment Pharmacol Ther* 2007;25:681-92.
- ¹² Corazziari E, Attili AF, Angeletti C. et al. Gallstones, cholecystectomy and irritable bowel syndrome (IBS) MICOL population-based study. *Dig Liver Dis* 2008;40:944-50.
- ¹³ Parslow TG: Immunogens, antigens, & vaccines. In: Parslow TG, Stites DP, Terr AI, Imboden JB, ed. *Medical Immunology* 10th Ed, New York: Lange Medical Books/McGraw-Hill Medical Publishing Division; 2001: 72-81.
- ¹⁴ Sampson HA: Food Allergies. In: Feldman M, Friedman LS, Brandt LJ, ed. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease* 9th Ed, Saunders Publishing, 2010: 139-14

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/s/

LARA DIMICK-SANTOS
07/17/2012

RUYI HE
07/17/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202-811

Applicant: Forest & Ironwood

Stamp Date: 8/9/2011

Drug Name: Linaclotide

NDA/BLA Type: 505 (b)(1)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			electronic CDT
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			Module 2.5
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Module 5.3.5.3
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Module 5.3.5.3
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Module 2.5
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505(b)(1)			
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: MCP-103-202 Sample Size: 309 (28days) Arms: 72ug (59 subjects), 145ug (56), 290ug (62), 579ug (63), PBO (69) AND Study Number: MCP 103-005 Sample Size: 36 Arms 100mg (12), 1000mg (12), placebo (12) Effect on GI transit time	X			A Phase 2b, double blind, randomized, placebo controlled Parallel group, dose-ranging safety, efficacy, and dose response of multiple doses of Linaclotide

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Location in submission: Mod: 5.3.5.1				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Yes Pivotal Study #1 MCP-103-302 IBS-C Indication: Treatment of Pivotal Study #2 LIN-MD-31 IBS-C Indication: Treatment	X			A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial of Linaclotide Administered Orally for 26 Weeks in Patients with IBS-C A Phase III, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Trial of Linaclotide Administered Orally For 12 Weeks Followed by a 4-Week Randomized Withdrawal Period in Patients with IBS-C
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			N/A	212 centers in US, 8 centers in Canada
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			N/A	Because of linaclotide's limited systemic bioavailability, a thorough QT study was not performed. Based on recommendations received from QT-IRT consult (7/29/2008), triplicate ECGs were obtained on a cohort of patients in phase 2 and 3 trials

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			This is a NME and has never been marketed any where in the world
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			As of the 11 October 2010 cutoff date, 4370 patients (1627 CC and 2753 IBS-C) and 75 healthy subjects received at least 1 dose of linaclotide: <ul style="list-style-type: none"> • 909 CC and 1492 IBS-C patients were exposed for at least 6 months • 745 CC and 416 IBS-C patients were exposed for at least 12 months
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			N/A	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			Requested and submitted as a IR
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			N/A	NME – first in class - poorly absorbed so appears most SA are GI tract related, evaluation appears adequate at this time
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			All clinical trials requested were submitted CMC?
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			N/A	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			partial waiver requested: IBS-C patients

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					younger than 6 years of age and CC patients younger than 6 months of age. deferral requested: IBS-C patients ages ⁽ _b to 17 years and CC patients _b months to 17 years
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			N/A	Very low systemic exposure – with low abuse potential
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			N/A	212 centers in US, 8 centers in Canada
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			N/A	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			Module 1.3.4
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			No overall statement but one with each clinical trial report

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer – Lara Dimick-Santos, MD

Date

Clinical Team Leader – Ruyi He, MD

Date

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

/s/

LARA DIMICK-SANTOS
10/04/2011

RUYI HE
10/04/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202811

**Applicant: Ironwood
Pharmaceuticals, Inc**

Stamp Date: August 9, 2011

Drug Name: Linaclotide

NDA/BLA Type: 505(b)(1)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	XX			eCTD submission
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	XX			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	XX			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	XX			
5.	Are all documents submitted in English or are English translations provided when necessary?	XX			
6.	Is the clinical section legible so that substantive review can begin?	XX			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	XX			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	XX			Clinical Overview in Module 2.5
9.	Has the applicant submitted the integrated summary of safety (ISS)?	XX			ISS submitted by indication. For Chronic Constipation, ISS is located in Module 5.3.5.3.28
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	XX			ISE submitted by indication. For Chronic Constipation located in Module 5.3.5.3.27
11.	Has the applicant submitted a benefit-risk analysis for the product?	XX			Benefit-risk analysis included in clinical overview in Module 2.5
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				Application is a 505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: MCP-103-004 Study Title: A Randomized, Multicenter, Double-Blind, Parallel-design, Phase 2 Trial of Oral MD-1100	XX			Phase 1 dose-response studies were conducted in healthy study participants and in patients with IBS-C. Separate Phase 2 dosing studies were conducted in patients with IBS-C and CC.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<p>Acetate Administered for 14 Days once Daily at 100, 300, 1000µg or Placebo to Patients with Chronic Constipation Sample Size: 42 (enrolled) 36 evaluated Arms: 96µg linaclotide, 290µg linaclotide, 966µg linaclotide, 10µg placebo Location in submission: Module 5.3.5.1 (*Note: Linaclotide dose-strength expression changes were the result of changes in the analytical procedures for determining the linaclotide content in clinical trial material.)</p> <p>And</p> <p>Study Number: MCP-103-201 Study 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 Constipation Sample Size: 309 Arms: 72 µg, 145 µg, 290 µg, 579 µg linaclotide, placebo Location in submission: Module 5.3.5.1 (*Linaclotide dose-strength expression changes were the result of changes in the analytical procedures for determining the linaclotide content in clinical trial material)</p>				
EFFICACY					
14.	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p>Pivotal Study #1 MCP-103-303 A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-group Trial of Linaclotide Administered Orally for 12 weeks Followed by a 4 week Randomized Withdrawal Period in Patients with Chronic Constipation. Indication: Treatment of Chronic Constipation</p> <p>Pivotal Study #2 LIN-MD-01 A Phase 3, Randomized Double Blind Placebo-Controlled, Parallel-Group Trial of Linaclotide Administered Orally for 12 weeks in Patients with Chronic Constipation Indication: Treatment of Chronic Constipation</p>	XX			
15.	<p>Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the</p>	XX			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	applicant by the Division) for approvability of this product based on proposed draft labeling?				
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	XX			The proportion of 12-week CSBM overall responders who received Linaclotide will be compared with the proportion of responders in the placebo group using the CMH test. Responder was a patient who was a CSBM Weekly Responder for ≥ 9 of the 12 weeks of the Treatment Period) A Weekly responder was a patient who had a CSBM week frequency rate that was 3 or greater and increased by 1 or more from baseline.) No previous agreements mentioned during the pre-NDA meeting. Sponsor has included an analysis of the endpoint current accepted by the Division.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		XX		Of a total 212 study centers, all but 8 were in the U.S.. Eight centers were in Canada
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	XX			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?		XX		Per FDA Letter dated September 3, 2008, the Division concluded that because of linaclotide's limited systemic bioavailability, a TQT study was not required in the clinical program
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	XX			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	XX			Across all 13 trials for both IBS-C and CC, a total of 4370 patients received at least 1 dose of linaclotide as of October 20, 2010. Of

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					these patients, 1981 were patients with chronic constipation. At least 853 patients with chronic constipation were exposed to linaclotide for at least 6 months. At least 715 were exposed to linaclotide for a year.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			XX	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	XX			MedDRA version 13.0 used. Also coding is located in the ADAE dataset of the ISS
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			XX	This is a NME, first in class
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	XX			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?				Special CMC data may have been required.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			XX	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	XX			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	XX			Drug considered to have low abuse potential due to limited systemic availability.
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			XX	Only 8 Canadian studies were included in the submission, all other were US Sites
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	XX			

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	XX			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	XX			
34.	Are all datasets to support the critical safety analyses available and complete?	XX			Links in 5.3.5.3.25.3.1 do not work. Able to open dataset from definition file only.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	XX			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	XX			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	XX			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	XX			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	XX			Statement of Good Clinical Practice submitted with the individual CSRs

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? XX

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Erica L. Wynn, M.D., M.P.H.

September 21, 2011

Robert P. Fiorentino, M.D., M.P.H.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

ERICA L WYNN
09/28/2011

ROBERT FIORENTINO
10/04/2011