CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Division Director Review

Date	August 29, 2012
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA#	202-811
Applicant Name	Forest Laboratories and Ironwood Pharmaceuticals
Date of Submission	August 9, 2011
PDUFA Goal Date	September 9, 2012 (with 3 month extension)
Proprietary Name / Established (USAN) Name	Linzess/ (linaclotide)
Dosage Forms / Strength	Proposed: 290 mcg once daily for IBS-C (oral administration) 145 (b) (4) mcg once daily for CIC (oral administration)
Proposed Indication(s)	1. Treatment of irritable bowel syndrome with constipation (IBS-C) 2. Treatment of chronic idiopathic constipation (CIC)
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Lara Dimick, MD/Ruyi He, MD [IBS-C] Erica Wynn, MD, MPH/Robert Fiorentino, MD, MPH [CIC]
Statistical Review	Milton Fan, PhD/Mike Welch, PhD
Pharmacology Toxicology Review	Yuk-Chow Ng, PhD/David Joseph, PhD
CMC Review and Biopharmaceutics Review	Jane Chang, PhD/M. Kowblansky, PhD/Moo-Jhong Rhee, PhD/Terrance Ocheltree, PhD/Kareen Riviere, PhD/Sandra Suarez-Sharp, PhD
Clinical Pharmacology Review	Sandhya Apparaju, PhD/Sue-Chih Lee, PhD
Pedatric and Maternal Health Staff	Elizabeth Durmowicz, MD/Hari Sachs, MD/Jeanine Best, MSN/Melissa Tassinari, PhD/Lisa Mathis MD
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CDTL Review	Ruyi He, MD
OSE/DMEPA	Jamie Wilkins-Parker, Pharm.D./Carlos Mena-Grillas, R.Ph
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OSE/DEPI1	Christian Cao, MPAS, PA-C/Carolyn McClosky, MD, MPH
OSE/DRISK	Yasmin Choudary, M.D.
OMP/OPDP (Patient labeling)	Sharon Mills/Barbara Fuller, MSN
OMP/OPDP/DCDP	Eunice Chang-Davies/Kathleen Klemm
SEALD	Jeanine Delasko, MD/Eric Brodsky, MD/Laurie Burke, RPh, MPH

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DB7= Division of Biometrics 7
DMEPA=Division of Medication Errors Prevention and Analysis
DPV = Division of Pharmacovigilance
DSI=Division of Scientific Investigations
DRISK= Division of Risk Management
DTP=Division of Therapeutic Proteins
CDTL=Cross-Discipline Team Leader
OBP=Office of Biotechnology Products
OMP= Office of Medical Policy
OPDP=Office of Prescription Drug Promotion
PMHS=Pediatric and Maternal Health Staff
SEALD=Study Endpoints and Label Development

1. Introduction

The applicant proposes Linzess, a first-in class guanylate cyclase C (GC-C) receptor agonist, for two indications: IBS-C (irritable bowel syndrome – constipation predominant) and CIC (chronic idiopathic constipation). The product and its metabolite are so minimally absorbed in humans that serum levels of the parent could only be detected in pharmacokinetic studies at supratherapeutic doses and the metabolite could not detected. Activation of GC-C at the luminal surface of the intestine causes an increase of intracellular and extracellular cGMP, which activates the cystic fibrosis transmembrane conductance regulator (CFTR), leading to secretion of chloride and bicarbonate. This results in increased intestinal fluid. The extracellular cGMP is proposed to have antinocioceptive effects through decreasing mechanosensitivity of splanchnic high-threshold colonic pain afferents.

I concur with the reviewers' recommendations to approve both indications. The major efficacy review issues for this NDA that I will cover in my review included: 1) (b) (4) and 2) which primary and secondary efficacy analyses should be included in product labeling for both indications.

There were two major safety issues: 1) determining how the evidence of deaths in neonatal/juvenile mouse studies should impact the product's pediatric development and labeling, and 2) assessing the potential for and impact of immunogenicity. The underlying cause/pharmacological effect that led to the nonclinical study finding of lethality within 1-2 days after first dose could not be identified. For this reason, it was not clear at what age it would be safe to administer Linzess to children. Although there was a strong hypothesis that the deaths could have been related to immature gut and to GC-C receptor density in neonatal mice, which suggested that the age of most concern for human exposure would be less than 2 years of age, insufficient evidence were available to establish this. In light of the unknowns, it was determined that the pediatric clinical studies should be delayed until additional animal data could be obtained and evaluated to establish the underlying cause of the lethality. In addition, the reviewers concluded the product should be contraindicated in children up to 6 years of age, and the product label should have a boxed warning stating the product's use should be avoided in children ages of 6 years and older.

The reviewers from Division of Therapeutic Proteins (DTP) in the Office of Biotechnology Products (OBP) were consulted regarding the need for further immunogenicity evaluation of Linzess. They determined that although Linzess is a small peptide, it has multiple attributes that make it potentially immunogenic, including its 3 disulphide bonds, which render a more rigid tertiary structure than is typical for a 14 amino acid peptide and an amino acid number that is in the ideal range to be a (b) (4) Because linaclotide has structural homology to endogenous guanylin peptides, the OBP reviewers raised concerns that the development of anti-drug antibodies could lead to deficiency syndromes related to cross reaction with endogenous guanylin peptides. They recommended PMRs to develop anti-drug antibody assays and to test patient samples for the presence of these antibodies.

2. Background

In this section I will provide the historical, regulatory context for the primary endpoints (and their definitions) selected for the major trials submitted in this NDA. In addition, I will provide the regulatory history for the patient-reported secondary endpoints (b) (4)

Constipation is a component of both indications proposed by the applicant. The Rome III Diagnostic Criteria for Functional Gastrointestinal Disorders describe the following diagnostic criteria for "Functional Constipation" (which must be present for the prior 3 months with onset at least 6 months prior to diagnosis):

1. Two or more of the following:
    a. Straining during at least 25% of defecations
    b. Lumpy or hard stools in at least 25% of defecations
    c. Sensation of incomplete evacuation for at least 25% of defecations
    d. Sensation of anorectal obstruction/blockage for at least 25% of defecations
    e. Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
    f. *Fewer than 3 defecations per week* [emphasis added].
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome.

The diagnostic criteria for IBS set forth in Rome III are two-fold and both must be met:

1. Abdominal discomfort or pain associated with two or more of the following at least 25% of the time
    a. Improvement of discomfort/pain with defecation
    b. Onset associated with a change in stool frequency
    c. Onset associated with a change in stool form (appearance)
2. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the symptoms

The key manifestation of IBS is abdominal pain/discomfort. For the IBS-C subtype, the abdominal pain/discomfort is associated with constipation (the defining change in stool associated with the pain/discomfort).

The pharmacological/physiological impact of Linzess on chloride and bicarbonate transport would be expected to change stool form and perhaps stool frequency through increasing fluid content of the stool. The relevance to humans of nonclinical studies of the product's impact on pain fibers is not established. For products to be considered therapeutically meaningful to treat the clinical entity IBS-C, the Division has recommended that development plans demonstrate an impact on both key components of IBS-C, i.e., constipation AND pain. The recently published Guidance for Industry Irritable Bowel Syndrome – Clinical Evaluation of Drugs for Treatment does state that the Division is willing to consider development plans for products intended to treat only one component of the IBS; however, each component must still be

studied and the product must be shown not to worsen the symptoms of the non-targeted component symptom/sign. Khan and Chang reported that pain is the symptom/sign of IBS that has been linked to impact on patients' quality of life, perception of disease severity, and health care utilization.[1] In this application, the clinical trials submitted to support the IBS-C indication were designed with primary endpoints that evaluated Linzess' impact on both constipation and abdominal pain.

The 4 major trials submitted to support both the IBS-C and CIC indications utilized definitions of constipation comparable to the definition described above. The constipation endpoint for both programs was complete spontaneous bowel movements (CSBM). Spontaneous bowel movements (SBM) are defined as bowel movements that occur without taking a laxative. Assessment of whether a spontaneous bowel movement was "complete" was accomplished by asking a patient to characterize each bowel movement, in response to the question, "Did you feel like you completely emptied your bowels?" Although the Rome Criteria diagnostic criteria do not require that the bowel movements are associated with a sensation of incomplete evacuation, it is one of the potential defining criteria. Since for this criterion >25% of bowel movements must have associated sensation of incompleteness, even patients for whom this is a key diagnostic criterion would not necessarily have this sensation with all their bowel movements. Khan and Chang reported that a sensation of incomplete evacuation is common in IBS. The Guidance for Industry Irritable Bowel Syndrome – Clinical Evaluation of Drugs for Treatment utilizes CSBM to define populations for study entry and for defining treatment response (as did the Draft Guidance).

The primary endpoint of the two CIC trials was proportion of CSBM responders. To be considered a responder patients had to achieve at least 3 CSBMs per week AND an increase of at least 1 CSBM above baseline for at least 9/12 weeks on study. For the two IBS-C trials, there were 4 primary endpoints. The first primary was proportion of responders based on pain response AND CSBM response. The CSBM responder definition was the same as that utilized in the CIC trials. The second and third primary endpoints separated the pain and CSBM components of the first primary and examined them individually. The last primary endpoint definition was based on both pain and CSBM, but utilized both a smaller minimum number of weeks of response needed to be classified an overall responder (6/12 weeks instead of 9/12) and a less stringent requirement for number of CSBMs (only an increase of one CSBM above baseline instead of also requiring achievement of a minimum of 3 CSBMs/week).

With regard to the CSBM endpoints utilized in these trials, it should be noted that the ROME criteria don't absolutely require incomplete evacuation sensation to make a diagnosis of functional constipation, and they don't absolutely require that a patient have less than 3 bowel movements per week to be diagnosed with functional constipation. As summarized above, the key features selected for the defining the primary endpoint of the key trials in this NDA are among other criteria in the list of Rome diagnostic criteria, which don't all have to be met in a single patient. The Division has been recommending an entry criterion of less than 3 bowel movements per week in clinical trials of constipation treatments, and has moved toward utilizing CSBM as an endpoint because it seems a spontaneous bowel movement is most clinically meaningful for a patient if it is not associated with a sensation of incomplete

[1] Khan S and Chang L. Nat Rev Gastroenterol Hepatol. 7, 565-581 (2010): 565-581

evacuation. In light of reliance on number of bowel movements per week as an entry criterion, for CIC trials the Division has moved toward recommending that the responder definition should be achievement of the number of bowel movements per week that exceeds the number that defines trial eligibility. The current IBS-C Guidance, however, does not set the bar as high and only requires increasing the number of CSBMs per week by 1. The clinical relevance of this change in number of CSBMs has not been established.

Lubiprostone is the only product on the market currently approved specifically for treatment of CIC. Lubiprostone is also the only currently approved product for IBS-C. The trials that supported the approval of lubiprostone for CIC utilized an endpoint based on SBM (not CSBM), and the IBS-C clinical trial primary endpoint did not specifically characterize the drug's impact on bowel movements. The primary efficacy analysis in the lubiprostone CIC trials was a comparison of SBM frequency. The primary efficacy analysis in the IBS-C trials was a comparison of a global symptom relief question, "How would you rate your relief of IBS symptoms (abdominal discomfort/pain, bowel habits, and other IBS symptoms) over the past week compared to how you felt before you entered the study?" A monthly responder was defined as a response to that question of "significantly relieved" for at least 2/4 weeks of the month or "moderately relieved" for all 4 weeks of the month. A patient also had to be a monthly responder for at least 2/3 months on study to be considered an overall responder. A responder definition based on a global question has significant limitations. A global question does not delineate what specific symptoms are being impacted by the product, and the comparison to baseline over time is problematic because patients are being asked to rely on recall over long time periods for comparisons. Although the current Guidance encourages utilization of a global question to help explore clinical meaningfulness of incremental changes in various changes in signs/symptoms over time, these global questions should be designed in such a way that patients rate their current overall symptoms. That score can then be compared to the baseline score in response to the same question.

Regulatory History of the CIC Development Plan

The discussions between the applicant and FDA regarding protocol design issues for the CIC clinical development are documented in an appendix to Dr. Erica Wynn's clinical review. The meeting minutes from a May 15, 2008 end of phase 2 (EOP2) meeting clearly document that the Division agreed to the applicant's proposal to use CSBMs in defining a responder, and to require that a patient had to have at least 3 CSBMs in a week PLUS an increase of at least 1 CSBM over baseline to be considered a responder (in at least 9/12 weeks on treatment). The Division also encouraged the applicant to include a question to provide information on how the patient viewed the change in bowel movements they experienced with treatment, in order to better assess whether the responder definition reflected a meaningful change from the patient perspective. The FDA recommended that the protocol incorporate a patient rating of change question to quantify the patient's assessment of improvement.

In November 2008, the sponsor sent a letter to the Division referencing the May 15, 2008 EOP2 meeting. Their approach to establish content validity and psychometric properties of the CIC secondary endpoints was described, as follows:

1) Prepare a white paper based on literature review regarding patient reported symptoms of chronic constipation and PRO measures previously used in linaclotide phase 2b chronic constipation studies and in phase 3 trials.
2) Conduct iterative sets of in-depth individual interviews with patients to establish the content validity of PRO measures for use in the phase 3 trials
3) Evaluate the psychometric properties of the current set of PRO measures selected for use in phase 3, using data from the phase 2 CIC trial.

The sponsor stated they would welcome FDA's comments on the interview methodology and that they looked forward to sharing the results. The interview description indicated that they would conduct 3 iterative sets of qualitative interviews in a target sample of 30 individuals with CC to identify the "full complement and relative importance of CC symptoms and treatment outcomes" and to insure the wording and response scales of the PRO items being considered for use in the clinical trials are appropriate and easily understood. The general interview approach was described. The sponsor stated that "If the results of the patient interviews indicate that one or more clinically important symptoms are not being assessed in the ongoing phase 3 trial, PRO items measuring these symptoms will be added to the phase 3 trials in consultation with the Agency. The use of data related to such added endpoints in the linaclotide label would be left to the discretion of the Agency."

With regard to the psychometric analysis, the sponsor reinforced that the data tested would be from the phase 2 CIC trial (MCP-103-201). The summary report would be prepared and submitted in the NDA. The "anticipated" analyses included reliability, construct validity, discriminating ability, responsiveness, and minimally important difference estimation. The sponsor planned to use the response of "somewhat relieved" on the global relief item ("Compared to before you started this study, how would you rate your constipation during the past 7 days?") to determine the latter.

There is no record of subsequent interaction with the Agency regarding the PROs after receipt of this letter. It appears from this letter that the intent of the interviews was to determine whether any additional items would be added to the clinical trials during their conduct. The key psychometric evaluation of the PRO endpoints and assessment tools were not intended to be submitted until time of the NDA. There is significant risk in not gaining agreement on the psychometric properties of these measures prior to initiation of phase 3 trials.

Regulatory History of the IBS-C Development Plan

The interaction between FDA and the applicant regarding the IBS-C endpoints included an EOP2 meeting on August 7, 2008, in which the sponsor proposed the primary endpoint for the IBS-C trials would be a 12-week CSBM overall responder defined as a CSBM weekly responder for 9/12 weeks. A CSBM weekly responder would be a patient who had achieved at least 3 CSBMs per week and had an increase by at least 1 CSBM/week compared to baseline. The Division didn't agree and said that other major manifestations of IBS-C should be part of the primary endpoint. The FDA recommended developing an instrument based on patient input. The instrument should be shown to represent "a complete, meaningful, appropriate, and interpretable instrument of the major manifestations of IBS-C" for use as the primary endpoint. In the meeting, the sponsor said that they would submit a new study design and

information to support a co-primary endpoint of abdominal pain and constipation. In addition, the sponsor said it would "submit information from their qualitative studies to support the use of their proposed PRO instruments."

Correspondence from the FDA dated May 20, 2010 (in response to an IND amendment dated April 20, 2010) stated that the FDA did not agree with the sponsor's proposal to change the definition of weekly CSBM responder (for IBS-C) from the original proposal to only an increase of at least 1 CSBM per week from the baseline. The amendment was triggered by the publication of the Draft IBS Guidance. The FDA stated that because the Guidance was only draft, the recommendations might change. The Agency pointed out that the applicant had not presented data in their submission that the definition of response, as revised, is meaningful to patients. In accordance with the Draft guidance, the sponsor had also proposed to change the responder definition from 9/12 weeks to 6/12 weeks. The Agency also cautioned against this change, and stated that if the sponsor changed the responder definition they should analyze the data using both the original and revised definitions.

The Final Guidance, published May 2012, recommends the following provisional IBS-C endpoints:

Table 2. Summary of Recommended Provisional Primary Endpoints,* Entry Criteria, and Responder Definition

Indication	Primary Endpoints	Entry Criteria	Responder Definition
IBS-C		**Abdominal Pain Intensity**	**Abdominal Pain Intensity**
	Abdominal Pain Intensity	Weekly average of *worst abdominal pain in past 24 hours* score of ≥ 3.0 on a 0 to 10 point scale	Decrease in weekly average of *worst abdominal pain in the past 24 hours* score of at least 30% compared with baseline
	AND	AND	AND
	Stool Frequency	**Stool Frequency**	**Stool Frequency**
		< 3 CSBMs per week	Increase of 1 or more CSBM per week compared with baseline

The Guidance states that FDA recommends the development of a multi-item PRO instrument that captures all the clinically important signs and symptoms of the IBS-C population. Acknowledging the time that it takes to develop an appropriate instrument, the Guidance provided for the provisional endpoints summarized above, for use in the interim until the necessary PRO instrument becomes available. The Final Guidance recommends use of the same responder definition that the IBS-C protocols submitted in this NDA included as one of the 4 primary endpoints.

Regulatory History Specific to Secondary Endpoints – CIC and IBS-C

The numerous secondary endpoints evaluated in the clinical trials supporting both indications were discussed during meetings and in correspondence during development. Because these endpoints were subject to significant discussion during labeling negotiations, presubmission agreements specific to secondary endpoints are summarized below.

At the IBS-C EOP2 meeting, the sponsor asked for agreement that results of (b) (4) The FDA did not agree and recommended that the sponsor establish the relationships between each item and the overall concept of IBS-C and develop a single comprehensive instrument for assessing treatment effect.

At the CIC EOP2 meeting, the sponsor proposed to include 7 secondary endpoints in the phase 3 trials, and proposed that the results could be included in labeling if the findings were statistically and clinically significant. FDA stated an instrument should be developed based on patient input, to assure that what was measured was a meaningful, complete and appropriate measure of constipation. The applicant said it would try to identify such an instrument. If one was not available, they would consider performing qualitative studies in the target population and developing a new instrument that represents a composite of the important signs and symptoms of chronic constipation, with evidence of content validity. The Agency encouraged the sponsor to keep FDA "abreast of their instrument development as it unfolds so that FDA can provide recommendations." The minutes indicate that the Agency then stated that the concepts measured by an instrument that measures the signs and symptoms of constipation and has evidence of content validity may be delineated in the product label "if appropriate."

The applicant included weekly questions during the CIC and IBS-C trials that were intended to capture patients' rating of the meaningfulness of the response they experienced. The responses to the questions were intended to provide an anchor upon which a determination of the clinical meaningfulness of change (e.g., change of number of bowel movements defining responder) could be determined. The IBS Guidance states the following regarding inclusion of questions in development programs to achieve this goal:

> "The global assessment should ask patients to evaluate only their current IBS status and not compare their current IBS signs and symptoms to another point in time, such as baseline status. Examples of such assessments include the following questions, which could be asked of patients on a weekly basis:
>
> □ "How would you rate your abdominal pain overall over the past 7 days?"
>
> □ "How would you rate your constipation (for IBS-C) or diarrhea (for IBS-D) overall over the past 7 days?"
>
> □ "How would you rate your IBS signs or symptoms overall over the past 7 days?"
>
> Sponsors can consider Likert scale response options, such as: **2** = Significantly Relieved, **1** = Moderately Relieved, **0** = Unchanged, **-1** = Moderately Worse, and -**2** = Significantly Worse"

The above Likert response options were included in some of questions asked of patients in the CIC and IBS-C trials. In the context of the current review, it appears that the suggested Likert

responses provided in the Guidance may be inappropriate, because they imply comparison to a previous time period, which not only is not specified, but could be interpreted to mean baseline. These points from the Guidance become relevant in interpreting the applicant's findings of statistically significant results for many tested "concepts" as secondary efficacy endpoints in the trials submitted to support this NDA. The FDA did not provide feedback prior to NDA submission on the psychometric analyses that the sponsor conducted to support inclusion of the specific questions and instruments utilized in the clinical trials to capture patient outcomes for a number of the secondary endpoints proposed for product labeling.

3. CMC

I concur with the conclusions reached by the chemistry reviewers that sufficient information was provided in the NDA to assure identity, strength, purity, and quality of the drug product. All manufacturing site inspections were acceptable, and all labeling issues identified by the CMC reviewer were resolved.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology reviewers recommended approval, and I concur. The nonclinical findings in neonatal/juvenile mice described in this section resulted in specific revisions in the applicant's proposed label (Boxed Warning, Contraindication, and revisions to Section 8.4 Pediatric Use), a requirement to conduct postmarketing safety studies under FDAAA, and impacted the initiation of the pediatric development plan. (See Section 10 Pediatrics of this review.)

The Pharmacology reviewers noted that the toxicology studies conducted in mice for qualification of linaclotide degradants (b) (4) revealed no significant differences in adverse effects between linaclotide vs. spiked (with degradants) linaclotide. The unspiked linaclotide control was a dose of 20 mg/kg/day.

Linaclotide was negative in the Ames test and in in vitro chromosomal aberration assay in human peripheral blood lymphocytes. The CAC determined that the product is not tumorigenic in rats or mice.

I concur with the Pharmacology reviewer's review findings regarding maternal and embryo-fetal development studies. In light of the fetal morphology effects observed in mice, a model in which significant maternal toxicity (lethality) was observed, I concur with the reviewer's recommendation to include Pregnancy Category C language in the product label.

Neonatal/Juvenile Mice Studies

Oral toxicity studies in neonatal/juvenile mice revealed that this model was extremely sensitive to linaclotide. Lethality was observed in a dose-ranging study at 50 micrograms/kg per day when dosing was started at post partum day 7, 100 micrograms/kg/day when dosing was started at 14 days post partum and 600 micrograms/kg/day when dosing was started at 21 days post partum. All of the deaths occurred within 24 hours after the first dose. The Pharmacology reviewers observed that these data indicate that the dose leading to lethality was dependent on age of the young mouse. Older juveniles tolerated doses that caused lethality in the younger mice. The minimum lethal dose is approximately twice the proposed human adult

dose, based on microgram/kg dosing. The cause of death could not be determined. The applicant hypothesized that the increased expression of intestinal guanylate cyclase-C in young animals was the likely mechanism, however, clinical evidence of increased watery stool production and weight loss suggestive of excess fluid loss were lacking. The sponsor also suggested that the deaths may be related to an immature GI system. Toxicokinetic data revealed no consistent detection of linaclotide or its metabolite.

Another neonatal/juvenile mouse study submitted for review started dosing at 7 days post partum (youngest animals tested in the previous study) with a plan to dose x 9 weeks. In this study the minimum lethal dose was 10 micrograms/kg/day. (The 50 microgram/kg dose from the previous study was not included in this study.) Five of 40 animals treated at that dose died and the deaths occurred within 24-48 hours post start of dosing. Animals that survived the initial few days of dosing completed the study without signs of toxicity. The minimum lethal dose in 7-day old mice is approximately twice the proposed human adult dose, based on microgram/kg dosing. The original study design included a high dose of 30 micrograms/kg/ day, however this dose was removed early after study initiation due to lethality (100%) in the toxicokinetic group given this dose.

The sensitivity to linaclotide exhibited by neonatal/juvenile mice was not observed in adult mice. Although lethality was observed in adult mice in various repeat dosing studies described in more detail below, the NOAEL in a 26-week oral toxicity study in adult mice was 20,000 microgram/kg/day. The reviewers reported that mortality occurred in adult pregnant mice at 40,000 micrograms/kg/day and at doses of at least 80,000 micrograms/kg/day in non-pregnant animals. Toxicokinetic data suggest higher exposures in female mice than males.

The Pharmacology reviewers recommended approval. They pointed to the age dependence of mouse lethality, and suggested that even though a mechanism could not be firmly established for the lethality, a safe dose could be estimated for older human children. Although I understand that the reviewers made their recommendations based on our usual scientific paradigm for establishing safe starting doses for human studies, I could not agree that we have adequate evidence available to embark on pediatric trials with confidence that the safety of children will be adequately protected. My concerns about initiating pediatric trials, even in older age groups, based on the usual methods for estimating safe doses from nonclinical studies included: 1) the toxicity in neonatal/juvenile mice was death, and the death was rapid in onset, 2) the underlying cause of the death could not be established, 3) because the cause of death could not be established, the applicability of this observation to human children could not be determined, and without the underlying cause, the age of applicability in human children could not be defined. Although there was a strong hypothesis that this observation is related to guanylate cyclase-C receptor density and/or age dependent gut integrity, which could help guide selection of a safe pediatric population for study, this hypothesis has not yet been proven. Adult studies have established the safety profile of the product, and while it seems extremely unlikely that a 16 year old would tolerate the product differently, without understanding the mechanism of lethality in these mouse studies, it is difficult for me to justify the risk of initiating studies in an older pediatric age group at this time. In light of the existence of alternative therapies for the constipation and IBS in children, I could not conclude that the risk/benefit supported initiation of pediatric studies in any age group until the

underlying cause of death in young mice had been delineated. For these reasons, I would recommend clinical hold of human pediatric trials until this issue is adequately resolved.

Adult Animal Toxicity Studies

The adult animal data are presented below to provide context for the observations described above in the neonatal/juvenile mice studies. A 26-week oral toxicity study in adult mice identified a NOAEL of 20,000 micrograms/kg/day. A 13-week oral study in adult rats identified a NOAEL of 50,000 micrograms/kg/day in males and 100,000 micrograms/kg/day in females. A 39-week oral toxicity study in Cynomolgus monkeys identified a NOAEL of 5000 micrograms/kg/day. Toxicokinetics suggest higher linaclotide exposures in non-mouse models.

13- Week Mouse oral: There were deaths in a 13-week oral toxicity study in mice. Dose levels were 20, 100 and 200 mg/kg/day. The deaths in this study were summarized in the following tables, which are reproduced from the Pharmacology/Toxicology review. There were 33 premature deaths in the 100 and 200 mg/kg/day groups. The target organs were kidneys, spleen, stomach, colon and heart.

Mortality in Main Study and Recovery Groups After Day 7		
Dose (mg/kg/day)	**Deaths**	**Day(s)**
0	1/20 males	74
20	none	
100	3/10 males 5/10 females	68, 88, 88 83, 88, 88, 89, 89
200	6/20 males 6/20 females	9, 84, 87, 88, 88, 89 9, 9, 37, 54, 82, 88

Mortality in Toxicokinetic Groups After Day 7		
Dose (mg/kg/day)	**Deaths**	**Days**
0	2/20 females	8, 27*
20	2/20 males 2/20 females	8, 29 31, 31
100	1/20 males 3/20 females	83 71, 74, 83
200	1/20 males 2/20 females	67 9, 31

*Animal died after blood collection.

Animals Replaced After Death on Days 1-7 (Main Study, Recovery, and Toxicokinetic Groups)	
Dose (mg/kg/day)	**Deaths**
0	1 female
20	2 females
100	2 males 7 females
200	4 males 17 females

Clinical signs in the 100 and 200 mg/kg/day groups included tremors, convulsions, absent or reduced feces, cold skin. Slow breathing occurred in the 200 mg/kg/day group. There were no clinical signs in the low dose (20 mg/kg) group.

Hematological changes were noted (decreased Hgb and Hct), increased reticulocyte count, increased WBC count, increased neutrophils, lymphocytes, monocytes and eosenophils.

Histopathology in the premature death group revealed (in 1-2 animals each):

200mg/kg: subcapsular adrenal hyperplasia, cecal ulceration, lymphohistiocytic inflammation, single cell necrosis in tubules and tubular hyperplasia in the epididymis, myocardial degeneration, lymphohistiocytic inflammation and necrosis, proximal tubular necrosis, tubular epithelial hypertrophy, hepatic inflammatory changes with multifocal necrosis, pulmonary hemorrhage, arterial thrombosis and bronchiolar epithelium apoptosis, nerve fiber degeneration, pharyngeal muscle degeneration and neutrophilic inflammation, stomach ulcers, hemorrhage and apoptosis, seminiferous tubule necrosis, and thymic cortical atrophy, vacuolar degeneration in pars distalis of the pituitary.

100 mg/kg: lymphoid necrosis in Peyers patches, lymphoid depletion and lymphoid necrosis in the spleen, gastric ulcers.

The reviewer noted that there were deaths in the 0 and 20 mg/kg/day groups, 4 and 6 mice respectively: however, histopathologic evaluation wasn't performed on any of those animals.

The histopath examination of the mice that were terminally sacrificed included the following findings (1-2 mice per 12-14 group):

200 mg/kg: gallbladder epithelial hyperplasia and neutrophilic inflammation, cardiac mineralization, kidney mineralization, sciatic nerve fiber degeneration, Peyers patch lymphoid necrosis, skeletal muscle lympohistiocytic inflammation, skin neutrophilic inflammation, splenic lymphoid depletion, gastric inflammation with ulcer, thymic cortical atrophy and lymphoid hyperplasia.

100 mg/kg: cardiac and kidney mineralization, hepatic vacuolization.

The toxicokinetics for 200 mg/kg in this study are summarized in the table below, which is reproduced from the Pharmacology review. The drug was not detectable in the 20 mg/kg group and "was sporadically detected" in the 100 mg/kg group.

Toxicokinetic Parameters for MD-1100 Acetate

Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-2} (ng•hr/mL)	AUC_{0-t} (ng•hr/mL)
		Day 1			
200	M	39.8	1.00	49.4	86.0
	F	50.0	0.500	51.2	51.2
		Day 27			
200	M	38.7	0.500	38.4	25.7
		Day 85			
200	M	27.9	0.500	39.0	39.0
	F	28.7	2.00	24.0	24.0

Values were determined from 3 mice/sex/time-point.

26-week Mouse oral toxicity study: Doses were 0, 5, 20, or 100/80 mg/kg/day. The dose in the last group was initiated at 100 mg, but reduced to 80 mg due to mortality in the first week. The numbers of animals found dead are summarized in the table below, which is reproduced from the Pharmacology review:

Table 2: Animals Found Dead (Days 1-7) in a 26-week Oral Toxicity Study in Mice

	Main Study Group Animals Found Dead (M/F)	Toxicokinetic Group Animals Found Dead (M/F)
0 mg/kg/day	0/0	0/0
5 mg/kg/day	0/1	0/5
20 mg/kg/day	1/2	2/5
100/80 mg/kg/day	2/9	11/10

Clinical observations in the animals that died included decreased activity, hunched posture, cold skin, difficulty breathing. Gavage was the cause of death in 3 females in the 20 mg/kg/day group and 3 males and 1 female in the 100/80 mg/kg group. One female in the 100/80 group had severe chronic glomerular and tubular disease. Other animals found dead or euthanized had autolysis of the urinary bladder (2/3 and 4/4 females in the 20 and 100 mg groups, respectively), autolysis in the spleen (3/3 and 3/4 females in the 20 and 100/80 mg/kg groups, respectively) and diffuse lymphoid atrophy (3/3 males in the 100/80 mg/kg group).

Hematological findings (not limited to animals that died) revealed reduction in platelet counts, increased reticulocytes, increased neutrophils, reduced monocytes.

Histological findings included:

100/80 mg/kg: kidney multifocal medullary mineralization, focal acute pulmonary hemorrhage, diffuse lymphoid atrophy, splenic multifocal increased hematopoiesis, focal submucosal lymphocytic infiltration of bladder [all in 2-4/12-14 animals]

The toxicokinetic data over time are summarized in the table below, reproduced from the Pharmacology review. Exposure to the metabolite was lower than the parent (see Pharmacology review for the summary table.)

Table 11: Toxicokinetic Parameters of Linaclotide Analyzed in a 26-week Oral Toxicity Study in Mice

Dose (mg/kg/day)	Day	Gender	t_{max} (h)	C_{max} (ng/mL)	C_{max}/D	AUC_t (ng h/mL)	AUC_{0-2} (ng h/mL)	AUC_{0-24} (ng h/mL)
5	1	Female	1.0	3.017	0.603	1.495	3.003	3.003
		Male	1.0	1.150	0.230	0.566	1.141	1.141
	90	Female	1.0	24.367	4.873	6.499	18.682	18.682
		Male	0.5	0.988	0.198	0.553	0.670	0.670
	180	Female	0.5	0.481	0.096	0.553	0.553	0.913
		Male	0.5	1.003	0.201	0.564	0.690	0.690
20	1	Female	1.0	7.710	0.386	9.724	7.764	11.484
		Male	1.0	6.780	0.339	7.492	7.492	8.376
	90	Female	0.5	3.577	0.179	4.305	4.305	4.954
		Male	0.5	2.807	0.140	6.942	3.956	8.202
	180	Female	4.0	19.350	0.968	25.138	5.090	63.838
		Male	0.5	5.913	0.296	5.382	5.382	7.148
100/80	1	Female	2.0	86.900	0.869	432.580	97.525	432.580
		Male	0.5	28.200	0.282	62.082	33.645	99.276
	90*	Female	1.0	648.793	6.488	553.717	499.790	758.517
		Male	0.5	16.800	0.168	18.673	12.100	23.289
	180*	Female	2.0	16.840	0.168	44.761	24.654	48.625
		Male	1.0	196.980	1.970	162.214	156.795	163.366

Notes: NC = not calculated, * = dose was 80 mg/kg/day, NA = not applicable

13-week Rat oral toxicity study: There was a single death at the 100 mg/kg dose level considered possibly drug related but the cause was not determined at necropsy. The NOAEL in males was 50 mg/kg/day and 100 mg/kg/day in females. No target organs of toxicity were identified. WBC's were increased. Toxicokinetics are summarized in the table below to facilitate comparisons to the mouse studies in which numerous deaths occurred. The Cmax at 100 mg/kg in rats appears comparable to the Cmax at 200 mg/kg dose leveling the 13 week oral mouse toxicity study. Comparison to the 26 week mouse study is difficult because of the widely disparate Cmax values reported in the 100/80 mg/kg dose group of that study.

Toxicokinetic Parameters for MD-1100 Acetate in Rat Plasma

Dose Group	Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-t} (ng·hr/mL)	AUC_{0-4} (ng·hr/mL)
			Day 1			
3	50	M	9.36	0.500	6.88	11.3
		F	6.97	0.500	9.14	11.6
4	100	M	24.0	0.500	28.7	36.0
		F	300	0.500	174	174
			Day 27			
3	50	M	4.51	1.00	NC	NC
		F	6.48	1.00	8.32	11.4
4	100	M	18.8	0.500	21.0	24.3
		F	15.9	0.500	19.5	23.7
			Day 85			
3	50	M	4.52	0.500	2.92	4.23
		F	15.2	0.500	9.16	12.3
4	100	M	23.2	0.500	27.7	38.8
		F	33.5	0.500	43.5	72.3

Values were determined from 3 rats/sex/group/time-point.

14-Day Cynomolgus monkeys nasogastric: In a 14 day nasogastric administration study in Cynomolgus monkeys the NOAEL was 0.5 mg/kg/day. At 2.5 and 5 mg/kg/day there was liver toxicity, manifested by increased serum ALT after 2 weeks of treatment; however, there were no histopathology changes in the liver.

13-Week Cynomologus Monkey Oral study: Doses were 5, 10 or 50 mg/kg/day. One male in the 10 mg/kg/d group was sacrificed in moribund condition on day 32. Necropsy findings included evidence of dehydration and emaciation. The monkey had red watery colon contents, necrosis of renal proximal tubules, atrophy of gastric epithelium, mucosal degeneration in the colon, esophageal epithelial desquamation with colonization by bacteria and fungus, lymphoid depletion in spleen and lymph nodes, diffuse atrophy of the thymic cortex, bone marrow hypoplasia.

Monkeys had dose dependent watery feces. Hemoglobin and Hct were reduced in the 50 mg/kg/day recovery group. Hematuria occurred in one female (10 mg/kg) and one male (50 mg/kg). Hemoglobinuria was noted in 2 females in the 50 mg/kg group.

Histopathology findings for the animals sacrificed included:

50 mg/kg: (the following occurred in single animals) cecal submucosal inflammation, duodenal focal mucosal hemorrhage, ileo-cecal junction hemorrhage, cataracts, renal parenchymal hypoplasia, sclerotic glomeruli with fibrosis of surrounding tissue, skeletal muscle lymphohistiocytic inflammation.

10 mg/kg: cataracts (1)

The following tables summarize the toxicokinetics at 3 time points: day 1, month 1 and week 13. The Cmax at the 50 mg/kg dose level exceeds the range of exposure that produced toxicity in mice. Metabolite exposures were higher than the parent. The summary tables for the metabolite can be found in the Pharmacology review.

Summary of Toxicokinetic Parameters for MD-1100 Acetate in Male and Female Cynomolgus Monkey Plasma: Day 1

Dose Group	Dose Level (mg/kg)	Sex		C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	AUC_{0-4} (ng•hr/mL)	AUC_{0-24} (ng•hr/mL)	$AUC_{0-\infty}$ (ng•hr/mL)	$t_{1/2}$ (hr)
2	5	M	Mean	8.78	1.00	18.4	24.9	24.9	NA	NA
			SD	6.47	0.71	NA	NA	NA	NA	NA
			N	4	4	2	2	2	0	0
		F	Mean	12.8	0.500	19.2	25.1	25.1	NA	NA
			SD	7.8	0	NA	NA	NA	NA	NA
			N	3	3	2	2	2	0	0
3	10	M	Mean	11.7	1.00	25.6	27.6	34.9	52.6	1.57
			SD	7.8	0.71	12.0	10.4	12.2	NA	NA
			N	4	4	4	4	4	1	1
		F	Mean	9.81	0.875	14.6	18.6	18.6	NA	NA
			SD	3.88	0.750	2.6	4.1	4.1	NA	NA
			N	4	4	3	3	3	0	0
4	50	M	Mean	41.9	1.57	132	110	168	158	1.82
			SD	18.0	1.24	48	27	60	NA	NA
			N	7	7	7	7	7	1	2
		F	Mean	88.5	0.786	250	207	284	265	1.51
			SD	37.5	0.267	82	64	90	79	0.23
			N	7	7	7	7	7	7	7

Summary of Toxicokinetic Parameters for MD-1100 Acetate in Male and Female Cynomolgus Monkey Plasma: Week 4

Dose Group	Dose Level (mg/kg)	Sex		C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	AUC_{0-4} (ng•hr/mL)	AUC_{0-24} (ng•hr/mL)	$AUC_{0-\infty}$ (ng•hr/mL)	$t_{1/2}$ (hr)
2	5	M	Mean	10.5	0.500	19.3	22.6	25.7	NA	NA
			SD	7.3	0	NA	NA	NA	NA	NA
			N	4	4	2	2	2	0	0
		F	Mean	5.23	0.625	9.66	13.5	13.5	NA	NA
			SD	2.26	0.250	NA	NA	NA	NA	NA
			N	4	4	2	2	2	0	0
3	10	M	Mean	17.8	0.625	47.2	41.8	62.0	NA	2.65
			SD	13.0	0.250	42.3	26.8	54.7	NA	0.39
			N	4	4	4	4	4	0	3
		F	Mean	8.56	0.625	18.5	21.4	24.1	NA	NA
			SD	2.23	0.250	10.1	7.6	12.2	NA	NA
			N	4	4	3	3	3	0	0
4	50	M	Mean	56.6	1.36	174	137	214	NA	1.49
			SD	26.8	1.28	86	61	117	NA	0.13
			N	7	7	7	7	7	0	4
		F	Mean	107	0.643	228	200	260	NA	1.53
			SD	67	0.244	118	88	130	NA	0.38
			N	7	7	7	7	7	0	6

Summary of Toxicokinetic Parameters for MD-1100 Acetate in Male and Female Cynomolgus Monkey Plasma: Week 13

Dose Group	Dose Level (mg/kg)	Sex		C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	AUC_{0-4} (ng•hr/mL)	AUC_{0-24} (ng•hr/mL)	$AUC_{0-\infty}$ (ng•hr/mL)	$t_{1/2}$ (hr)
2	5	M	Mean	7.14	0.625	12.2	16.1	16.1	NA	NA
			SD	3.44	0.250	NA	NA	NA	NA	NA
			N	4	4	2	2	2	0	0
		F	Mean	12.5	0.500	19.3	26.1	26.1	NA	NA
			SD	5.9	0	6.4	8.0	8.0	NA	NA
			N	4	4	3	3	3	0	0
3	10	M	Mean	22.2	0.500	38.6	41.8	48.1	NA	1.72
			SD	17.6	0	40.2	37.5	48.5	NA	NA
			N	3	3	3	3	3	0	1
		F	Mean	26.9	0.642	64.4	54.4	89.7	NA	3.37
			SD	10.5	0.283	75.2	40.5	110.7	NA	NA
			N	4	4	4	4	4	0	1
4	50	M	Mean	54.1	0.714	148	131	173	NA	1.60
			SD	16.7	0.267	84	57	96	NA	0.26
			N	7	7	7	7	7	0	6
		F	Mean	71.1	0.655	168	148	191	NA	1.47
			SD	30.5	0.265	83	60	90	NA	0.17
			N	7	7	7	7	7	0	6

39-Week Cynomolgus Monkeys Oral toxicity study: Doses were 5, 10 or 50 mg/kg/day. Two deaths were attributed to drug – one at 10 mg/kg and one at 50 mg/kg. Both monkeys had watery feces, low food consumption, lethargy and hunched appearance. Histopathology revealed colonic mucosal necrosis, lymphoid depletion in lymph node and spleen, thymic cortical atrophy and pancreatic zymogen depletion. The other monkeys experienced watery feces but no other significant findings. The parent drug toxicokinetics are summarized below (the metabolite summary data can be found in the Pharmacology review; the metabolite AUC was higher than parent AUC). Cmax at the 50 mg/kg level was in range of or exceeded the Cmax associated with the 200 mg/kg dose level in the 13-week mouse study.

Table 22: Mean Toxicokinetic Parameters of Linaclotide in the 39-week Oral Toxicity Study in Monkeys

Dose (mg/kg/day)	Day	Gender	$t_{1/2}$ (h)	t_{max} (h)	C_{max} (ng/mL)	AUC_t (ng h/mL)	AUC_{0-24} (ng h/mL)	$AUC_{0-\infty}$ (ng h/mL)
5	1	Female	4.32 (1.53)	1.50 (0.577)	4.27 (0.985)	20.7 (1.65)	32.0 (5.02)	30.2 (6.89)
		Male	3.54 (1.36)	2.50 (1.00)	3.80 (1.40)	19.7 (5.89)	29.1 (8.01)	23.5 (5.69)
	89	Female	4.64 (1.86)	1.63 (1.60)	7.08 (4.14)	36.2 (23.1)	44.0 (18.2)	NA
		Male	1.83 (0.717)	0.875 (0.750)	5.88 (2.47)	13.5 (2.86)	16.7 (3.92)	NA
	222	Female	2.85 (0.37)	1.50 (0.58)	6.0 (3.2)	29 (18)	39 (24)	NA
		Male	3.23 (1.05)	1.75 (0.500)	8.00 (4.92)	35.5 (22.4)	49.8 (32.2)	NA
10	1	Female	2.83 (1.92)	2.00 (1.41)	11.5 (3.93)	50.8 (10.5)	67.9 (19.5)	54.8 (10.1)
		Male	4.27 (2.63)	3.00 (1.15)	8.71 (3.93)	57.1 (31.5)	72.8 (23.7)	80.0 (26.1)
	89	Female	2.07 (1.09)	0.625 (0.250)	18.2 (7.26)	52.9 (16.9)	61.6 (13.6)	NA
		Male	2.90 (1.52)	2.17 (1.76)	20.2 (24.2)	48.5 (28.3)	71.4 (36.0)	NA
	222	Female	2.41 (1.06)	0.750 (0.289)	21.7 (14.9)	75.8 (40.2)	94.8 (50.5)	NA
		Male	3.98 (1.60)	1.67 (0.577)	10.4 (6.41)	57.2 (36.5)	81.4 (50.6)	NA
50	1	Female	2.75 (1.17)	1.33 (1.33)	48.9 (25.2)	182 (49.4)	236 (68.5)	235 (39.9)
		Male	2.97 (0.665)	1.50 (1.34)	46.0 (23.9)	242 (178)	294 (164)	302 (169)
	89	Female	4.29 (3.00)	1.25 (1.37)	80.3 (50.7)	309 (219)	342 (208)	NA
		Male	2.14 (0.685)	1.08 (0.736)	70.2 (46.5)	196 (82.6)	239 (98.2)	NA
	222	Female	3.77 (2.53)	1.90 (1.34)	109 (76.9)	618 (355)	656 (355)	NA
		Male	3.42 (1.26)	2.00 (1.64)	47.9 (14.7)	229 (60.5)	292 (48.1)	NA

NA = not applicable; standard deviation presented in parentheses

5. Clinical Pharmacology

The Clinical Pharmacology reviewers found the application acceptable for marketing approval, with incorporation of their recommended changes in the proposed product labeling.

The highest proposed linaclotide dose for labeling is 290 micrograms/day, taken on an empty stomach 30 minutes prior to the first meal of the day. The pharmacokinetic data for linaclotide were obtained from two ascending dose studies in healthy volunteers (one single dose fasting and one multiple dose fasting) in which 30, 100, 300, 1000 and 3000 micrograms were administered, and a food effect study in healthy volunteers in which 300 micrograms were administered for 7 days (along with a 3000 microgram dose at the end of the second treatment period. Sparse pharmacokinetic sampling was also performed in the phase 3 trials (in which no dose exceeded 290 micrograms/kg/day). The limit of detection of linaclotide and its metabolite was 3 ng/mL in the assays used by the applicant for the initial PK characterization of linaclotide. In both the single dose and multiple dose studies (excluding the food effect study), linaclotide and its metabolite were not detected, even at the highest doses tested. The phase 3 trial pharmacokinetic sampling revealed no detectable drug in the patient populations studied. The assay for PK analysis of those trials had a lower limit of quantification of 2 ng/ml for both linaclotide and its metabolite.

In the food effect study (healthy volunteers; maximum dose of 3000 micrograms/kg), which utilized an assay with detection down to 0.2 ng/mL for linaclotide and 2 ng/ml for its active metabolite, serum levels were detected in a few subjects. The drug was administered daily x 7 days in each treatment period (fasting and fed), which were separated by a 21 day washout period. At the end of the second treatment period, a 3000 microgram/kg dose was administered as a single dose. Eighteen subjects received the high dose on the final day of the second period and 2/18 had detectable linaclotide levels at one or more time points after the 3000 microgram/kg dose. Cmax was 0.735 and 0.212 ng/mL in those two subjects. Linaclotide was detected in one sample from one subject, and 5 samples from the other. The metabolite was not detected in either. Both were in the fasted treatment period.

In light of the lethality observed in neonatal/juvenile mice studies described in Section 4 above, the Clinical Pharmacology reviewers strongly recommended that the applicant be required to conduct a clinical trial to characterize the amount of linaclotide and its active metabolite found in human milk as a postmarketing requirement under 505(0)(3). This trial will be conducted in healthy, lactating but non-nursing women. In the EOP2 meeting for the IBS-C indication on August 7, 2008, the applicant asked whether the Agency agreed with their contention that a clinical PK trial to test for distribution into breast milk would not be technically feasible and that the theoretical risk could be "appropriately communicated in labeling." The FDA responded "we cannot advise you until we have adequate information on the systemic exposure associated with the final to-be-marketed formulation." The pharmacokinetic data submitted in this application do in fact indicate that human absorption of linaclotide at the doses proposed for marketing is negligible (and undetectable, see pharmacokinetic data summarized below); however, it is theoretically possible that linaclotide could be concentrated in human milk. It is important to document that this is not the case. This will be a PMR clinical trial under FDAAA since death was seen in the neonatal/juvenile

mouse studies. Refer to Section 10 Pediatrics for information on labeling decisions regarding this issue.

There was no thorough QT (tQT) study submitted in this NDA because of the low human systemic exposures to linaclotide and its metabolite. At the May 15, 2008 EOP2 meeting for the CIC indication the sponsor asked if FDA agreed that it was unnecessary to perform a tQTc study with linaclotide "because linaclotide has a highly-localized distribution and qualifies as a drug for which the recommendations in the ICH E14 guidance might not apply." The Agency didn't agree for the following reasons: 1) linaclotide is a new molecular entity with limited experience in humans 2) nonclinical studies in animals have shown systemic effects and 3) the details of the potential systemic bioavailability of linaclotide and its metabolites are still under investigation. The Division stated that it would consult with the QT-Interdisciplinary review team (QTIRT) and contact the sponsor with an update. A consult response from the QTIRT, dated July 29, 2008, stated that a tQT was not necessary due to the evidence of lack of documentable systemic bioavailability at the doses intended for human therapeutic use. The consult pointed out that in the subjects treated with supratherapeutic doses in whom linaclotide was detected (2/18), the highest linaclotide concentration was <1 ng/ml which is <70 pmol. The consultants noted that exposures of potent inhibitors of hERG are typically in nmol concentrations.

Subsequent correspondence from the Division on September 3, 2008 informed the sponsor that a tQT study was not needed. Collection of ECGs in the phase 3 trials was recommended. The applicant performed ECGs in a subset of patients in the 4 randomized, controlled trials submitted to establish the efficacy of linaclotide (both CIC and IBS-C populations). There were 5 patients (of whom 3 were placebo arm patients) who had a QTC interval >500 msec. There were 8 patients with an increase in QTc from baseline of ≥60 msec (3 of whom were on placebo arms). The Clinical reviewers determined that these ECGs did not reveal a clinically relevant QT effect at the doses recommended for treatment of these conditions.

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.

In light of low systemic exposure, I concur that there is no need for further evaluation of QTc effects.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The applicant submitted two randomized, placebo controlled trials to support the efficacy of Linzess for each of the proposed indications, CIC and IBS-C. I have discussed the primary endpoints in Section 2 Background of this review. The efficacy results for each indication are presented below.

Chronic idiopathic Constipation (CIC)

The two phase 3 trials submitted in support of the CIC indication were Study LIN-MD-01 and Study MCP-103-303. Two Linzess dose levels were evaluated in each trial, 133 microgram/day and 266 microgram/day. These doses correspond to an actual linaclotide dose of 145 micrograms and 290 micrograms. Numerical differences were due to changes made in the analytical method for determining potency during product development. The 133 µg product tested in the clinical trials actually contained 145 micrograms of linaclotide, and the 266 microgram product tested in clinical trials actually contained 290 micrograms. The results for the primary efficacy analysis, 12- week CSBM overall responder for each trial are summarized in the tables below. In Study LIN-MD-01, there appeared to be some level of a dose response; however, in Study MCP-103-303, there was not even a trend of dose response. The primary analysis was the difference in responder rate by Cochran-Mantel-Haenszel (not the Odds ratios).

Table I: Primary Efficacy Analysis LIN-MD-01: 12-Week CSBM Overall Responders (ITT)

	Placebo (N = 215)	*Linaclotide*	
		133 µg/day (N = 213)	*266 µg/day (N = 202)*
Responder, n (%)	13 (6.0)	34 (16.0)	43 (21.3)
Nonresponder, n (%)	202 (94.0)	179 (84.0)	159 (78.7)
Difference in responder rate (linaclotide – placebo)	—	9.9	15.2
Odds ratio (95% CI)	—	2.93 (1.50, 5.72)	4.22 (2.20, 8.10)
p-Value	—	0.0012	< 0.0001

A 12-week CSBM overall responder was a patient who was a CSBM weekly responder for at least 9 of the 12 weeks of the double-blind treatment period.

Odds ratios were estimated using the Mantel-Haenszel method controlling for geographic region.

p-Values were obtained from the Cochran-Mantel-Haenszel tests controlling for geographic region, comparing each linaclotide dose versus placebo in a pairwise manner.

Both p-values 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.

Data source: Table 14.4.1.1

Table II: Primary Efficacy Analysis MCP-103-303: 12-Week CSBM Overall Responders (ITT)

Description	Placebo (N=209) n (%)	Linaclotide 133 ug (N=217) n (%)	Linaclotide 266 ug (N=216) n (%)
Responder	7 (3.3)	46 (21.2)	42 (19.4)
Non-Responder	202 (96.7)	171 (78.8)	174 (80.6)
Difference in Responder Rate (Linaclotide - Placebo)		17.8	16.1
Odds Ratio for Response (Linaclotide : Placebo)		7.72	7.21
95% CI for Odds Ratio		(3.41, 17.47)	(3.14, 16.59)
P-value		< 0.0001	< 0.0001

Data Source: Section 14, Table 14.4.1.1
A 12-week CSBM Overall Responder is a patient who was a CSBM Weekly Responder for at least 9 of the 12 weeks of the Treatment Period. A CSBM Weekly Responder is a patient who had a CSBM weekly frequency rate that was 3 or greater and increased by 1 or more from baseline
n = Number of patients within a specific category.
CI = Confidence interval
Odds ratios were estimated using the Mantel-Haenszel method controlling for geographic region.
P-values were obtained from the CMH tests controlling for geographic region, comparing each linaclotide dose versus placebo in a pairwise manner.
Both p-values met the criterion for statistical significance based on the MCP.

The Statistical reviewers conducted sensitivity analyses to evaluate the impact of missing data and concluded the observed efficacy findings were robust.

The Clinical reviewers have recommended [redacted] (b) (4) I agree with their recommendation.

The statistical analysis plan provided testing of the highest dose first, and if found statistically significant, testing could proceed to the lower dose arm and 5 secondary endpoints in the high dose arm (6 hypotheses, using overall type I error of 0.05 and Hochberg procedure to control for multiplicity). Those prioritized secondary endpoints were:

1) Change from baseline in 12-week CSBM **frequency**
2) Change from baseline in 12-week SBM **frequency**
3) Change from baseline 12-week stool consistency
4) Change from baseline in 12-week straining severity
5) Change from baseline in 12-week constipation severity

If appropriate, testing could then proceed to 3 additional secondary efficacy parameters in the high dose arm (again testing by means of Hochberg with an overall type I error of 0.05):

6) Change from baseline in 12-week abdominal discomfort

7) Change from baseline in 12- week bloating.

If appropriate the first group of secondary endpoints would then be tested for the low dose arm, followed by testing of the second group of secondary endpoints in the low dose arm.

All secondary endpoint analyses were statistically significant. The prespecified analysis of these secondary endpoints was change from baseline over the 12 week treatment period, utilizing multivariate ANCOVA modeling, which the statistical reviewers considered problematic due to model-based assumptions. The applicant's secondary endpoint analyses data tables presented in the FDA Statistical review present the mean and median data over the 12 week period from this multivariate ANCOVA analysis approach. The applicant also conducted the analyses of change from baseline at week 12 that limited the comparison to the week 12 data (adjusting for baseline), which was considered a more appropriate approach from the FDA Statistical Reviewers' perspective for end-of-study comparison, and these were also associated with p values <0.05. However, there were questions regarding the clinical meaningfulness of some of changes that were found to be statistically significant. In addition, there were questions regarding the adequacy of the delineation of the PRO concept being evaluated and the scoring systems utilized to measure some concepts, including bloating and abdominal discomfort.

In the presentation of secondary endpoint analyses that follow, I have utilized the applicant's prespecified ANCOVA analysis (referred to as "Treatment overall" in the applicant's tables), which utilizes all the data over the 12 weeks, and does not limit the comparison to the 12 week and baseline values (which, as stated above, was considered the most appropriate analysis by the FDA Statistical reviewers). I have done so because it was the prespecified analysis. For secondary endpoint change from baseline outcomes that were included in labeling, I have also included the results of the FDA preferred analysis.

For the change in CSBM frequency rate secondary endpoint analysis, the baseline median number of CSBMs in all arms of both trials was 0, and the mean ranged 0.26-0.28 in LIN-MD-01 and 0.24-0.33 in MCP-103-303. The maximum baseline value was 1.95 – 2.43 in LIN-MD-01 and 1.95-2.9 in MCP-103-303. The 12 week mean frequency rate was 0.9 in the placebo arm of both trials, and increased to 2.25 and 2.93 in the Linzess arms of LIN-MD-01, and to 2.38 and 2.39 in MCP-103-303. The 12-week Linzess medians were approximately 1 CSBM less than the means. Although the mean change is statistically significant, and the responder analysis which required achieving at least 3 CSBMs per week at 12 weeks, resulted in a significant difference between Linzess and placebo, when the mean number of CSBMs per week is examined the group mean at 12 weeks still falls under 3 CSBMs per week (the definition of constipation at study entry).

In light of the variable use of CSBM vs. SBM in previous development plans, it is of some interest to compare the baseline CSBM frequency rate in these trials with the baseline SBM rate. The mean baseline SBM frequency in LIN-MD-01 was 1.8-1.9 (median 1.5-1.9) and in MCP-103-303 it was 2.0-2.1 (median 1.5-1.9). The trials data for CSBM and SBM are presented in the same table below to facilitate comparisons of results when the two definitions of bowel movements are utilized. The CSBM cells include a calculation, in parentheses, for

the percent of SBMS at each data point the CSBMS represent. The proportion of SBMS that are CSBMS increases with treatment in all arms (including placebo), but the increase is greatest in the Linzess arms. The increase in proportion is greater for means than for medians.

Table III: Comparison of CSBM and SBM data in LIN-MD-01 and MCP-103-303

LIN-MD-01				
		Placebo	**Linzess 133**	**Linzess 266**
Baseline	**Mean CSBM**	0.27 (15% of SBMs)*	0.26 (14% of SBMs)	0.28 (14% of SBMs)
	Median CSBM	0	0	0
	Mean SBM	1.82	1.85	1.94
	Median SBM	1.45	1.46	1.91
Treatment Overall**	**Mean CSBM**	0.90 (30% of SBMs)	2.25 (43% of SBMs)	2.94 (52% of SBMs)
	Median CSBM	0.32 (13% of SBMs)	1.29 (28% of SBMs)	1.82 (37% of SBMs)
	Mean SBM	2.97	5.29	5.65
	Median SBM	2.51	4.59	4.88
MCP-103-303				
Baseline	**Mean CSBM**	0.33 (16% of SBMs)	0.33 (17% of SBMs)	0.24 (12% of SBMs)
	Median CSBM	0	0	0
	Mean SBM	2.05	2.13	2.01
	Median SBM	1.93	1.94	1.47
Treatment Overall**	**Mean CSBM**	0.91 (28% of SBMs)	2.38 (45% of SBMs)	2.39 (57% of SBMs)
	Median CSBM	0.32 (10% of SBMs)	1.66 (33% of SBMs)	1.54 (36% of SBMs)
	Mean SBM	3.21	5.24	5.09
	Median SBM	3.22	4.98	4.34

***The percentages are the percentage of SMBs that were CSBMS, based on corresponding values (medians or means) for baseline and with treatment. ** Applicant's prespecified ANCOVA analysis data.**

In Study LIN-MD-01, the proportion of SBMs that were CSBMs doubled on the placebo arm, whereas the proportion quadrupled on the Linzess arms. In Study MCP-103-303, the proportion of mean SBMs that were CSBMs nearly doubled on the placebo arm, whereas the proportion tripled and more than quadrupled in the Linzess arms.

Patients were asked global assessment questions to interpret/explore clinical meaningfulness of observed treatment changes. The questions utilized in the trials included a weekly question, "Compared to before you started this study, how would you rate your constipation symptoms during the past 7 days?" This question requires a comparison to baseline over an extended time on study. The study question regarding constipation severity "on average, how would you rate your constipation during the past 7 days?" overcomes the comparison flaw, but asks the patient to average symptoms. The question never specifically refers to severity, although the potential responses utilize qualitative words that correspond to degrees of severity (none, mild, moderate, severe, very severe; 1-5). At baseline in these studies the mean and median scores in response to this question were in the 3 range on all arms (moderate), whereas the overall treatment score dropped to low to mid 2 range (mild) in the Linzess arms and upper 2 range in the placebo arms. These data suggest that the changes in CSBM and SBM observed in these trials with Linzess treatment resulted in a shift from patients experiencing what they characterized as moderate constipation to mild constipation. However, this conclusion is based on looking at group mean/median data, not on examining the severity scores reported by patients who met the responder criteria vs. those who did not.

The applicant proposed to include narrative in the Clinical trials section of the label stating that Linzess had resulted in significant impact on (b) (4), stool frequency (CSBM and SBM), (b) (4) and stool consistency ("i.e., hardness of stool"). They also proposed (b) (4)

The reviewers agreed that the statements regarding stool consistency could be included because the instrument utilized by patients to assess stool consistency, the Bristol Stool Form Scale (BSFS), has been recommended for use in evaluating products intended to treat IBS (in the IBS Guidance). The BSFS was not utilized in these trials to specifically define constipation; however, the BSFS was used to exclude patients, i.e., if they had stool score of 6 (loose mushy) or 7 (watery) during the 14 days prior to starting treatment. Although the Rome Criteria do not designate a specific BSFS score as diagnostic of constipation, the criteria include a reference to "hard or lumpy stools." The BSFS utilizes the descriptor "lumpy" in scores 1 and 2. Score 3 refers to cracks, suggesting hardness. Score 4 utilizes the word "soft" in the descriptor. At baseline, the mean and median scores in the trials were greater than 2, but less than 3. The "Treatment overall" analyses of the BSFS scores revealed an improvement in scores in both the placebo and Linzess arms; however, the placebo arms shifted to a mean score of 3 (2.9 in LIN-MD-01), and the Linzess arms shifted to scores in the 4 range. The label includes a statement that Linzess resulted in significantly greater improvements

compared to placebo in stool consistency (as measured by the BSFS). The actual data are not presented in the label.

The reviewers also concluded that secondary endpoint information on 12 week CSBM and SBM was appropriate for labeling since these endpoints required only having patients report whether or not they had had a bowel movement, and the Division had already agreed to the concept of collecting CSBM data as part of the primary endpoint. The mean change from baseline at week 12 (1.5 CSBMs) was included, utilizing the analysis results recommended by the FDA Statistical reviewers. The mean change from baseline at week 12 analysis is restricted to the week 12 data. (The data in the label were not derived from the ANCOVA analysis prespecified by the applicant).

The Rome criteria for functional constipation refer to straining; however, the Division and SEALD have not agreed that the instrument and scale for capturing straining data is appropriately designed. In addition, it was not clear that the difference in changes observed were clinically meaningful. All patients had baseline scores in the 3 range (moderate amount), based on the scale (1-5, with 1= not at all and 5=extreme amount) used in the trial, in response to the question "How much did you strain during the bowel movement?" The mean scores shifted to the 2 range (a little bit) in all arms (including placebo) in both trials (high 2 range on placebo vs. low 2 range on the Linzess arms). Although the difference in change from baseline in both trials was statistically significantly different between placebo and Linzess, the difference seemed small. The least squares mean difference relative to placebo for the two Linzess doses were -0.587 and -0.654 in LIN-MD-01 and -0.606 and -0.637 in MCP-103-303. (b) (4)

(b) (4) The Division and SEALD have not agreed that the instrument and scale for capturing these data are appropriately designed. It is not clear whether these concepts are clearly and consistently understood by patients when presented in the instrument. It is not clear how the concept of abdominal discomfort is distinguished from bloating and/or abdominal pain. With regard to bloating, the changes from baseline in the trials were quite small in all arms, and the difference in change from baseline between placebo and the Linzess arms was also quite small [-0.209 and -0.261 in LIN-MD-01; -0.240 and -0.150 in MCP-103-303; on a scale of 1 to 5]. Despite their statistical significance, it was not clear that the differences were clinically meaningful. With regard to abdominal discomfort, even smaller differences (yet statistically significant) were observed between placebo and the Linzess arms [-0.185 and -0.215 in LIN-MD-01; -0.175 and -0.133 in MCP-103-303]. (b) (4) . Even if one accepted that the concepts were adequately justified, defined and measured, there was no persuasive evidence presented that these small differences are clinically relevant.

The applicant proposed (b) (4)

Irritable Bowel Syndrome – Constipation predominant (IBS-C)
The two phase 3 trials submitted in support of the IBS-C indication were Study MCP-103-302 and Study LIN-MD-31. Only one Linzess dose level was evaluated in each trial, i.e., 266 microgram/day (an actual 290 microgram dose). Due to changes made in the analytical method for determining potency during product development, it was determined that the "266 microgram" product tested in clinical trials actually contained 290 micrograms of linaclotide.

The results for the 4 primary efficacy analyses in each trial are summarized in the table below. Pooled analyses were not included because they were not pre-specified. The 4 primary endpoints were discussed in Section 3 Background of this review. The "9/12 APC 3+1 responder" refers to the responder definition in which a patient must have achieved at least 3 CSBMs **and** an increase of at least 1 CSBM above baseline **PLUS** have at least a 30% decrease in abdominal pain for at least 9 of 12 weeks of the treatment period. The "9/12 CSBM + 3 responder" drops the requirement of the pain response from the responder definition. Likewise, the "9/12 pain responder" definition drops the CSBM requirement from the definition. Finally, the "6/12 Week APC +1 Responder" returns to the combination definition, incorporating both pain and CSBM; however, patients did not have to achieve at least 3 CSBMs per week (only a minimum increase of 1 CSBM per week required) and the response only had to be present in at least 6 of 12 weeks.

Linzess was found to be superior to placebo in all 4 endpoints. Comparison of the response rates for each component of the "9/12 Week APC 3+1 responder" to each other and to the combined endpoint suggests that the limiting component of the combined responder definition (for both placebo and Linzess) was the requirement to have at least 3 CSBMS + 1 per week. The responder rate for 30% reduction in pain was relatively high in both placebo and Linzess compared to the CSBM response. The responder rate for CSBM 3+1 (9/12 analysis) was stable between trials in both the placebo and Linzess arms. Pain response appeared less stable between trials.

Table IV Overview of Phase 3 Primary Efficacy Parameter Results (ITT Population)

Primary Efficacy Parameters	**MCP-103-302**		**LIN-MD-31**	
	Placebo (N = 403)	***Linaclotide 290 ug (N = 401)***	**Placebo (N=395)**	***Linaclotide 290 ug (N = 405)***
9/12 Week APC 3 + 1 Responder				
Responder %	3.0	12.7	5.1	12.1
Odds Ratio (95% CI)		4.7 (2.4, 8.8)		2.6 (1.5, 4.5)
Difference in Responder Rate		9.7		7.0
9/12 Week CSBM 3 + 1 Responder				
Responder %	5.0	18.0	6.3	19.5

Primary Efficacy Parameters	MCP-103-302		LIN-MD-31	
	Placebo (N = 403)	***Linaclotide 290 ug (N = 401)***	**Placebo (N=395)**	***Linaclotide 290 ug (N = 405)***
Odds Ratio (95% CI)		4.2 (2.5, 7.0)		3.7 (2.3, 5.9)
Difference in Responder Rate		13.0		13.2
9/12 Week Abdominal Pain Responder				
Responder %	19.6	38.9	27.1	34.3
Odds Ratio (95% CI)		2.6 (1.9, 3.6)		1.4 (1.0, 1.9)
Difference in Responder Rate		19.3		7.2
6/12 Week APC +1 Responder				
Responder %	13.9	33.7	21	33.6
Odds Ratio (95% CI)		3.2 (2.2, 4.5)		1.9 (1.4, 2.7)
Difference in Responder Rate		19.8		12.6

The 6/12 Week APC + 1 primary endpoint (4th) analysis incorporated two changes from the other 3 endpoints. The applicant submitted additional analyses to facilitate interpreting differences in the outcomes observed with this endpoint definition vs. the other primary endpoints. The table that follows below presents these analyses.

When the change in definition of the 4th endpoint is isolated to the minimum number of weeks needed to be defined a responder, so that the 6/12 endpoint analysis also incorporates the 3 CSBMs component of the prespecified 9/12 primary endpoints (6/12 APC 3+1 vs. 9/12 APC 3+1), the delta for the difference between placebo and Linzess increases in the 6/12 week analysis relative to the 9/12 first primary; however, the increase is proportional in both the placebo and Linzess arms. The Odds Ratio for the 9/12 week APC 3+1 is similar to the Odds ratio for the same analysis for 6/12 week AP 3+1.

Examination of the difference in results between the 6/12 and 9/12 APC responder definitions when each only require 1 additional CSBM per week instead of CSBM 3+1 (6/12 APC+1 vs. 9/12 APC +1) reveals a similar delta between placebo and Linzess with these two analyses in MCP-103-302; however, in Study LIN-MD-31, the delta is numerically smaller in the 9/12 APC+1 analysis. The Odds Ratio is increased in the 9/12 APC+1 analysis of MCP-103-302 relative to the 6/12 APC+1 Odds ratio, and is stable between the 9/12 and 6/12 APC+1 analyses in Study LIN-MD-31. Both (6/12 and 9/12 analyses) result in higher rates of responders than if a minimum of 3 CSBMs per week is required.

Exploration of differences in observed results between 6/12 week and 9/12 week analyses when the responder definition is limited to only the CSBM+3 endpoint (leaving out

requirement of pain response) reveals the response rate increases in the 6/12 CSBM+3 analyses (compared to 9/12 CSBM+3), and there is a consistent treatment effect observed between trials for each time point (again suggesting the differences observed between trials are driven by the pain component of the responder definitions).

Table V: Exploratory Comparison of Outcomes between the 6/12 and 9/12 Week Responder Definitions When the Number of CSBMs Used in Each Definition is the Same

Responder Definitions	**MCP-103-302**		**LIN-MD-31**	
	Placebo (N = 403)	***Linaclotide 290 ug (N = 401)***	**Placebo (N=395)**	***Linaclotide 290 ug (N = 405)***
9/12 Week APC 3 + 1 Responder				
Responder %	3.0	12.7	5.1	12.1
Odds Ratio (95% CI)		**4.7** (2.4, 8.8)		**2.6** (1.5, 4.5)
Difference in Responder Rate		9.7		7.0
6/12 Week APC 3+1 Responder				
Responder %	6.2	22.4	9.9	23.0
Odds Ratio (95% CI)		**4.43** (2.76, 7.11)		**2.76** (1.84, 4.15)
Difference in Responder Rate		16.2		13.1
9/12 Week APC +1 Responder				
Responder %	5.5	22.7	10.6	17.8
Odds Ratio (95% CI)		**5.13** (3.13, 9.39)		**1.83** (1.21, 2.76)
Difference in Responder Rate		17.2		7.1
6/12 Week APC +1 Responder				
Responder %	13.9	33.7	21.0	33.6
Odds Ratio (95% CI)		**3.2** (2.2, 4.5)		**1.9** (1.4, 2.7)
Difference in Responder Rate		19.8		12.6
9/12 Week CSBM 3 + 1 Responder				
Responder %	5.0	18.0	6.3	19.5
Odds Ratio (95% CI)		**4.2** (2.5, 7.0)		**3.7** (2.3, 5.9)
Difference in Responder Rate		13.0		13.2
6/12 Week CSBM 3+1 Responder				

Responder Definitions	**MCP-103-302**		**LIN-MD-31**	
	Placebo (N = 403)	***Linaclotide 290 ug (N = 401)***	**Placebo (N=395)**	***Linaclotide 290 ug (N = 405)***
Responder %	9.4	29.4	12.7	31.9
Odds Ratio (95% CI)		**4.04** (2.71, 6.02)		**3.28** (2.27, 24.8)
Difference in Responder Rate		20		19.2

The Guidance currently recommends an endpoint that is equivalent to the fourth primary endpoint, 6/12 APC + 1, in the phase 3 trials submitted in this application. However, the first primary, 9/12 APC 3+1 seems more clinically meaningful, since it requires a more prolonged period of response and requires resolution of the entry criterion definition of constipation. Exploration of these various definitions of responders is of interest to examine the impact the rigor of the definition has on the observed treatment effect. With increasing "rigor" the proportion of responders decreases; however, in general, the Odds Ratios remain stable.

The trials included weekly IVRS questions on patients' assessment of constipation severity. They also asked patients to rate "IBS symptom severity," degree of relief of IBS symptoms, and assessment of adequate relief of IBS symptoms. The Clinical Reviewer of the IBS-C trials noted in her review that patients were asked to rate their overall relief of symptoms compared to baseline. As discussed in Section 2 Background of my review, the IBS Guidance indicates that, in general, patients should not be asked to compare their signs and symptoms to another point in time, such as baseline; however, the suggested question response wording in the Guidance does imply a comparison (e.g., "worse").

The Clinical reviewer presented an exploratory analysis of each of the primary efficacy responder definitions in which the average response to IBS global symptom relief questions was examined in the responders vs. nonresponders for each primary endpoint. As summarized in the clinical review, the following average score range was associated with the specific descriptors for degree of relief:

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.

The following tables, one from the clinical review that summarizes the data from these exploratory analyses and a second that I created to simplify comparisons of the PRCQ narrative ratings among endpoints, summarize the applicant's findings for responders and nonresponders.

Table 41: PRCQ and Degree of Relief Treatment Period Averages for the Primary Efficacy Parameters

Primary Parameter	*PRCQ Average (SD)*	*Degree of Relief of IBS Symptoms Average (SD)*
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

Responder Definition		**Anchor Rating For the Avg. PRCQ Score**
9/12 Week APC 3+1		
Responder		
	CSBM Frequency	Considerably relieved
	Abdominal Pain	Considerably relieved
Nonresponder		
	CSBM Frequency	Somewhat relieved
	Abdominal Pain	Somewhat relieved
6/12 Week APC +1		
Responder		
	CSBM Frequency	Somewhat relieved
	Abdominal Pain	Considerably relieved
Nonresponder		
	CSBM Frequency	Unchanged
	Abdominal Pain	Unchanged
9/12 CSBM 3+1		
Responder	CSBM Frequency	Considerably relieved

Responder Definition		**Anchor Rating For the Avg. PRCQ Score**
Nonresponder	CSBM Frequency	Unchanged
9/12 Abdominal Pain		
Responder		Considerably relieved
Nonresponder		Unchanged

These exploratory analyses demonstrate that for the various primary endpoint responder definitions, the responders' average score correlated with "considerably relieved" or "somewhat relieved," whereas the nonresponders' average score correlated with "somewhat relieved" or "unchanged." When the 6/12 APC+1 endpoint is compared to the 9/12 APC 3+1 endpoint, this exploratory analysis suggests with the shift to requiring a minimum of 3 CSBMs per week for 9/12 weeks from only requiring one additional CSBM for 6/12 weeks, patients have a greater sense of improvement with the more rigorous endpoint, at least for the bowel movement frequency component (considerably relieved vs. somewhat relieved).

These exploratory data are important to consider when reflecting on what responder definition is most meaningful from a clinical benefit standpoint to patients. However, they are only exploratory and there are problems inherent to relying upon patient responses that necessitate comparisons to a remote baseline. The PRCQ questions included patient rating of change questions for 7 IBS symptoms identified by the applicant. An example of a question is "Compared to before you started this study, how would you rate your abdominal pain at its worst during the past 7 days?" (1=Completely relieved, 1= considerably relieved, 3=Somewhat relieved, 4=Unchanged, 5+Somewhat worse, 6=Considerably worse, 7=As bad as I can imagine). This question asks for a comparison to baseline. The potential responses that correspond to the extremes appear capable of standing alone without comparison to baseline. For example, "as bad as I can imagine" appears to be a stand alone, non-comparative rating. Although responses 1 and 2 might be viewed as stand alone, "considerable relief" does imply a quantitative comparison. For this reason, for the verbatim question posed, the two extremes "complete relief" and "as bad as I can imagine" seem to be the most interpretable anchors. The average responses in the tables above did not fall into those extremes.

Secondary Endpoint Analyses IBS-C
The trials included 10 prespecified secondary endpoints:

1. Change from Baseline in 12-week CSBM Frequency Rate,
2. Change from Baseline in.12-week SBM Frequency Rate,
3. Change from Baseline in 12-week Stool Consistency,
4. Change from Baseline in 12-week Severity of Straining,
5. Change from Baseline in 12-week Abdominal Pain,
6. Change from Baseline in 12-week Abdominal Discomfort,
7 Change from Baseline in 12-week Bloating,
8 Change from Baseline in.12-week Percent of Abdominal Pain-free Days,
9. 6/12 Week CSBM +1Responder, and

10. 6/12 Week Abdominal Pain Responder.

These secondary endpoints are similar to those utilized in the CIC trials described above. The applicant's prespecified primary analysis of change from baseline was an analysis of covariance (ANCOVA) model over all treatment weeks with treatment group and geographic region as fixed-effect terms and the corresponding baseline value as a covariate. The least squares mean change from baseline for each treatment group was reported for each week, and described as "Overall treatment" effect. The FDA Statistical reviewers noted that the assumptions associated with this type of multivariate modeling over time cannot be readily supported, and for this reason, a preferred analysis is a univariate approach based on change from baseline at a specified week; the analysis based only on week 12 data is preferred for end-of-study comparisons. I have presented the applicant's prespecified primary analysis data in this review, but have added the results of the FDA preferred change from baseline analysis limited to the Week 12 data for the secondary analyses that were included in product labeling.

Only endpoints 5 and 8-10 were unique to the IBS-C trials. The Division's concerns regarding abdominal discomfort, bloating and severity of straining, which were described above in the CIC trial section, were also concerns in the IBS-C trial analyses.

The applicant proposed (b) (4)
(b) (4)
abdominal pain;
, stool frequency (CSBM (b) (4)

The reviewers agreed to include narrative information for the two secondary endpoints that constituted key components of the primary endpoints: 1) Change from Baseline in 12-week CSBM Frequency Rate and 2) Change from Baseline in 12-week Abdominal Pain (score, not percentage change). (b) (4)
. In addition, the percentage change from baseline in pain score was not a prespecified secondary endpoint. The reviewers agreed that the data for the absolute delta change in score from baseline, limited to the 12 week time point would be the most appropriate data for presentation. The Clinical reviewers pointed out that the average change in pain score and the average change in CSBM between Week 12 and baseline was relevant for inclusion in the label, since the responder analyses do not provide this granular information.

Based on the comparison limited to the Week 12 time point, for change in CSBM frequency, the difference between Linzess and placebo was approximately 1.5 CSBMs. The median number of CSBMs at baseline in all arms of both trials was zero, and the mean ranged 0.18-0.21 in MCP-103-302 and 0.20-0.24 in LIN-MD-31. (The maximum value documented at

baseline was 2.39 – 2.88 in MCP-103-302 and 2.43-2.9 in LIN-MD-31.) Utilizing the applicant's prespecified ANCOVA analysis, the "Treatment overall" 12 week mean frequency rate was 0.9 and 1.0 in the placebo arms of the two trials, and was 2.4 and 2.6 in the Linzess arms of the trials. Utilizing the ANCOVA analysis, the 12 week medians in the Linzess arms were approximately 1 CSBM less than the means (less than the difference observed with the FDA preferred analysis of change from baseline using only Week 12 data).

The secondary endpoint of change from baseline in abdominal pain score is important for understanding the response observed in these trials. The trial design, with regard to pain, was consistent with the Guidance in terms of eligibility (weekly average score of ≥ 3 on a 0-10 point scale) and responder definition (decrease in weekly average of worst abdominal pain the past 24 hours of at least 30% compared with baseline). "At least 30% reduction" does not provide granular information on the actual degree of pain relief experienced by patients in the trial. Change in pain score (group mean) from baseline provides this additional granularity. Based on calculation of change from baseline at Week 12, the difference between Linzess and placebo was approximately a decrease in 0.7 points on a 0-10 point scale. Patients had mean baseline pain scores in the range of 5.5-5.6 and medians in the range of 5.3-5.5. Utilizing the applicant's prespecified ANCOVA ("Treatment overall"), the mean scores decreased in both the placebo and Linzess arms of both trials, but the mean decrease was greater in the Linzess arms. The mean score ("Treatment overall") in the placebo arm was 4.4 in both trials, and the median was 4.1-4.2 in the two trials. On the Linzess arms, the mean score ("Treatment overall") was 3.7 in both trials, and the median was 3.3-3.4. The least squares mean difference relative to placebo was similar to the outcome observed with the FDA preferred analysis, -0.78 in MCP-103-302 and -0.74 in LIN-MD-31.

(b) (4)

The other secondary endpoin (b) (4) findings are briefly discussed below. The instrument utilized to measure the secondary endpoint of change from baseline in stool consistency, the Bristol Stool Form Scale (BSFS), has been recommended in the IBS Guidance for use in evaluating products intended to treat IBS-D (diarrhea predominant IBS). Although the Rome Criteria do not designate a specific BSFS score as diagnostic of constipation, the criteria include a reference to "hard or lumpy stools." The BSFS utilized as exclusion criteria in the IBS-C trials, i.e., patients were excluded if they had stool score of 6 (loose mushy) or 7 (watery) during the 14 days prior to starting treatment. The BSFS utilizes the descriptor "lumpy" in scores 1 and 2. Score 3 refers to cracks, suggesting hardness. Score 4 utilizes the word "soft" in the descriptor. Based on the applicant's prespecified ANCOVA analysis of change from baseline secondary endpoints, the "Treatment overall" analyses revealed an improvement in scores in both the placebo and Linzess arms; however, the placebo arms shifted to a mean score of 3 in both trials, and the Linzess arms shifted to scores in the 4.3-4.5 range. At baseline, the mean and median scores

in the trials were equal to or greater than 2, but less than 3 (mean 2.3 and median 2.0 in MCP-103-302; mean 2.3-2.4 and median 2.2 in LIN-MD-31).

One of the secondary endpoints (b) (4) was change in straining severity. The Rome criteria for functional constipation do refer to straining; however, the Division and SEALD have not agreed that the instrument and scale for capturing straining data is appropriately designed. In addition, it was not clear that the statistically significant difference in changes observed between placebo and Linzess were clinically meaningful. All patients had scores in the 3.5-3.6 range at baseline (3= moderate amount of straining and 4= a great deal of straining, based on the scale used in the trial). In the applicant's ANCOVA analyses, the mean scores shifted to the 2 range ("a little bit of straining") in all arms in both trials. The mean scores were in the high 2 range on placebo (2.8) vs. low 2 (2.1-2.3) range on the Linzess arms. The least squares mean difference between arms was -0.572 in MCP-103-302 and -0.655 in LIN-MD-31.

(b) (4) the secondary endpoint data for abdominal discomfort and bloating (b) (4) The Division and SEALD have not agreed that the instrument and scale for capturing these data are appropriate for use in registration trials. It is not clear whether these concepts are clearly and consistently understood by patients as presented in the instrument. It is also not clear what the concept of abdominal discomfort is relative to bloating and to abdominal pain. Abdominal pain, abdominal discomfort and bloating were all scored on an 11 point rating scale. In both trials, the baseline scores increased in magnitude as you move from abdominal pain to abdominal discomfort to bloating. The highest (worst severity) scores were in bloating. The on-treatment scores fell in both placebo and Linzess groups. The severity level of the "Treatment overall" (applicant's ANCOVA analysis) scores followed the same pattern as baseline scores (bloating scores higher than discomfort, and discomfort higher than pain). Based on the applicant's prespecified analysis, the numerically largest least mean square difference from baseline was in bloating score.

Table VI: Comparison of Pain, Discomfort and Bloating Scores in MCP-103-302 and LIN-MD-31

MCP-103-302		Placebo	Linzess 266	LS Mean Difference
Baseline	**Mean Pain**	5.5	5.6	
	Median Pain	5.3	5.4	
	Mean Discomfort	6.0	6.1	
	Median Discomfort	5.8	6.1	
	Mean Bloating	6.5	6.7	
	Median Bloating	6.5	6.6	
Treatment Overall*	**Mean Pain**	4.4	3.7	-0.782
	Median Pain	4.1	3.4	
	Mean Discomfort	4.9	4.1	-0.837
	Median Discomfort	4.8	3.9	
	Mean Bloating	5.5	4.7	-0.882
	Median Bloating	5.3	4.6	
LIN-MD-31				
Baseline	**Mean Pain**	5.6	5.7	
	Median Pain	5.4	5.5	
	Mean Discomfort	6.0	6.2	
	Median Discomfort	5.9	6.1	
	Mean Bloating	6.5	6.7	
	Median Bloating	6.4	6.9	
Treatment Overall*	**Mean Pain**	4.4	3.7	-0.74
	Median Pain	4.2	3.3	
	Mean Discomfort	4.7	4.1	-0.74
	Median Discomfort	4.6	3.8	
	Mean Bloating	5.3	4.6	-0.84
	Median Bloating	5.1	4.4	

***Applicant's prespecified ANCOVA analysis**

In light of the variable use of CSBM vs. SBM in previous development plans for products for IBS-C, it is of some interest to compare the baseline CSBM frequency rate in these trials with the baseline SBM rate. These data are of some interest when assessing whether the responder definition should be based on CSBM or SBM. A sensation of incomplete evacuation is not an

absolute requirement for diagnosis of IBS-C. In the table below I have summarized the baseline and "Treatment overall" CSBM and SBM data (from the applicant's prespecified ANCOVA analysis) for each study. In the CSBM data cells, I have provided the percentage of SBMs that the CSBM frequency represents for baseline and "Treatment overall", respectively. The mean baseline SBM frequency in MCP-103-302 was 1.7 (median 1.5) and in LIN-MD-31 it was 1.9 (median 1.5-1.9). The proportion of mean SBMs that were CSBMs (mean) at each time point (baseline and overall) increased in both arms of the studies. The increase in proportion was greatest with Linzess. In study MCP-103-302, the proportion of SBMs that were complete doubled on the placebo arm, whereas the proportion quadrupled on the Linzess arm. In Study LIN-MD-31 the proportion of mean SBMs that were complete nearly tripled on the placebo arm, whereas the proportion quadrupled in the Linzess arms. After baseline, the **placebo** SBM frequency rate approaches 3/week in one study and achieves 3/week in the other. Less than 3 bowel movements per week is one of the criteria for diagnosis of functional constipation. This suggests that relying on achieving 3 SBMs/week as a definition of responder in IBS-C would result in a high rate of placebo response.

Table VII: Comparison of CSBM and SBM data in LIN-MD-01 and MCP-103-303

MCP-103-302			
		Placebo	**Linzess 266**
Baseline	**Mean CSBM**	0.21 (12% of SBMs)*	0.18 (10% of SBMs)
	Median CSBM	0	0
	Mean SBM	1.7	1.8
	Median SBM	1.5	1.5
Treatment Overall**	**Mean CSBM**	0.88 (29% of SBMs)	2.37 (42% of SBMs)
	Median CSBM	0.25 (10% of SBMs)	1.42 (29% of SBMs)
	Mean SBM	2.99 (3.4 x)	5.70 (2.4 x)
	Median SBM	2.51 (10 x)	4.87 (3.4 x)
LIN-MD-31			
Baseline	**Mean CSBM**	0.24 (13% of SBMs)	0.20 (10% of SBMs)
	Median CSBM	0	0
	Mean SBM	1.90	1.94
	Median SBM	1.46	1.92
Treatment Overall	**Mean CSBM**	1.04 (33% of SBMs)	2.57 (43% of SBMs)
	Median CSBM	0.34	1.49

		(11% of SBMs)	(27% of SBMs)
	Mean SBM	3.17	5.98
	Median SBM	3.05	5.48

***Percentages are the percentage of SMBs that were CSBMS, based on corresponding values (medians or means) for baseline and with treatment. ** Applicant's ANCOVA analysis**

Questions included in the IVRS weekly reporting, included a "compared to before you started this study, how would you rate your constipation symptoms during the past 7 days?", which requires a comparison to baseline over an extended time period on study. A question regarding constipation severity "on average, how would you rate your constipation during the past 7 days?" was also asked. It didn't require a comparison to baseline, but asked the patient to average symptoms, which is generally not encouraged for PROs. The possible responses were none, mild, moderate, severe, very severe (scores 1-5). At baseline in these studies the mean and median scores in response to the latter question were in the 3 range on all arms (moderate), whereas the overall treatment score dropped to low to mid 2 range (mild) in the Linzess arms and upper 2 range in the placebo arms. These data suggest that the average changes in CSBM and SBM observed in these trials with Linzess treatment resulted in a shift from patients experiencing what they characterized as moderate constipation to mild constipation. However, this conclusion is based on looking at group mean/median data, not on examining the severity scores reported by patients who met the responder criteria vs. those who did not.

Summary. I concur with the reviewers that the major trials submitted in this NDA establish the efficacy of Linzess for treatment of CIC and IBS-C and support its approval. I agree (b) (4) the lower dose of Linzess studied in the CIC trials should be approved. (b) (4)

8. Safety

The most commonly reported adverse reaction was diarrhea, and it was most commonly reported in the first 4 weeks on study. Two Linzess dose levels were studied within the two CIC trials, which enabled within study comparisons of dose response as it related to adverse events, and the doses studied were associated with a similar proportions of patients who reported diarrhea and similar proportions who reported severe diarrhea. In the CIC trials, the proportion of patients with diarrhea was similar between males and females. In the IBS-C trials, a higher percentage of males developed diarrhea than females (15.6% vs. 6.5%). Half the patients who developed diarrhea as an adverse event did so within the first week of treatment.

In the pooled placebo controlled trial populations, for CIC 16% of the 145 microgram and 14% of the 290 microgram treated patients had adverse events of diarrhea (compared to 5% of placebo arm patients). One patient had dehydration and orthostatic hypotension, which were reported as SAEs, even though the diarrhea was not. Diarrhea was coded as severe in 15/129 patients with an AE of diarrhea in Linzess arms of the CIC phase 3 trials, and 36 (4% of the study population) discontinued treatment because of diarrhea. Four of the patients in the CIC

placebo controlled trials who had diarrhea also had adverse events of dehydration – 1 at the 145 microgram dose level and 3 at the 290 microgram level.

In the IBS-C phase 3 trials (in which only the 290 microgram dose was studied), 20% of patients reported an adverse event of diarrhea (vs. 3% of patients on the placebo arms). There were no SAEs related to diarrhea. Diarrhea was coded as severe in 16/160 patients with an AE of diarrhea, and 43 (5% of the study population) discontinued treatment due to diarrhea. Only one patient also had an adverse event of dehydration reported.

In the open label long term safety studies, nearly a third of patients (both CIC and IBS-C) reported diarrhea as an adverse event. Diarrhea was reported as severe in 3% of patients in the long term trials.

There were 7 SAEs with fatal outcome; however, 1/7 died during screening (without study drug exposure). None of the remaining 6 deaths were considered treatment related. Two of the deaths occurred more than 30 days post last dose. Two were due to malignancy (esophageal cancer and pancreatic cancer; the latter presented 8 days post starting Linzess). There were 3 deaths attributed to narcotic use. All these patients denied narcotic use at study entry. Two were in the IBS-C program (morphine; morphine + alprazolam) and one was in the CIC program (fentanyl). The Clinical reviewer for the IBS-C indication noted it was not clear whether the narcotic related deaths were intentional or accidental overdoses. One remaining death was attributed to injuries from a fall from a ladder. The Clinical reviewer noted that subject had a prior history of atrial fibrillation and syncope, and was taking multiple medications that could cause dizziness. The death occurred at 97 days on study.

Hepatic and Renal Adverse Events. Based on the clinical and histopathological findings in the nonclinical studies, the safety data should be examined for evidence of hepatic and renal toxicity. There were no patients in the placebo controlled trials (pooled IBS-C and CIC) who were discontinued for hepatic or renal toxicity, according to Table 55 in the Clinical Review for the IBS-C indication. However, the reviewers noted that there was one patient who discontinued Linzess for hypothyroidism and hepatic enzyme increase. Two placebo patients left the trials due to transaminase elevations. During the open label long term safety studies there were two patients (CIC) and 1 patient (IBS-C) who were discontinued due to hepatic enzyme elevation (total 3/3270 = 0.1%). None had laboratory findings consistent with Hy's law. There is no evidence of a signal of hepatic toxicity, which is consistent with the low systemic exposure observed in PK studies.

Elevated creatinine was documented in a similar proportion of patients across all study arms of the CIC trials (0.2 and 0.6% in the Linzess arms; 0.7% in the placebo arm). Dr. Dimick stated in her review that there were no notable changes in serum chemistry. The proportion of patients who developed creatinine levels >1.3 x ULN was 0.5% in both the linaclotide and placebo arms. In the long-term safety trials, elevated creatinine was reported in 0.6% CIC patients and 0.3% IBS-C patients. In light of similarities between Linzess and placebo in the randomized controlled trials, and the similar rate observed in the safety trials, there is no evidence of renal toxicity associated with Linzess in humans, at the doses administered in these trials. This is consistent with its low systemic exposure in PK studies.

Diverticular Events. Patients with a history of diverticulitis were excluded from participation in the phase 3 trials. There were 7 cases of diverticular events in patients exposed to Linzess (all events occurred in different patients): 2 diverticular perforations (patients in long term safety trial), one diverticular hemorrhage (in a phase 3 trial CIC patient treated with 290 micrograms) and 4 cases of diverticulitis in patients treated with Linzess. There was only one case of diverticulitis in a placebo patient. One of the Linzess treated cases of diverticulitis occurred in a patient in a phase 3 CIC trial, at a dose of 290 micrograms. Two of the diverticulitis cases occurred in CIC patients in the long term safety trials, and 1 case occurred in a patient with IBS-C in the long term safety trial. Considering that there were 1657 Linzess exposed patients in the phase 3 placebo controlled trials (combined CIC and IBS-C indications) and 3270 in the open label long term safety studies (combined CIC and IBS-C indications), these 7 cases represent a rate of approximately 0.2%, based on the total number of patients in the long term safety trial. [2/1657 = 0.1%; 5/3270 = 0.2%]

Strate, et al.[2] have reported that diverticulosis affects approximately 70% of people in the US ages 80 years and older, and that the number of patients affected by diverticular disease and its complications is rising. They noted that population-based cohort studies have indicated that the incidence of diverticulitis ranges 1-2%. The authors conducted their own cohort study of patients with documented diverticulosis detected on colonoscopy and found the cumulative probability of developing diverticulitis in patients with known diverticulosis was 4.3% (without CT confirmation) or 1% (CT or surgical confirmation). A figure in the Strate, et al publication (reproduced by them from Everhart, et al[3]) shows that in patients that undergo colonoscopy, diverticulosis is a very common finding. It increases with increasing age of patient at time of colonoscopy, from 20-35% in the 40-59 year age range, to approximately 50% in patients in their 60's, and over 60% in patients in their 70's. The median age in the phase 3 trials in this NDA was in the 40's. Using the lower percentage in the 40-59 year age range, the estimate for number of patients treated with Linzess who had diverticulosis in the placebo controlled trials is 331 and the estimate in the long term safety trials 654. This corresponds to diverticulitis rates among patients estimated to be actually at risk of 0.6% and 0.8%, respectively.

In light of the epidemiology, the observation of diverticular events in this NDA does not appear to represent a signal in the Linzess dataset. The fact that no cases were noted in placebo patients is worth noting; however, there were no placebo patients in the long term safety trials, which could explain the absence of placebo events.

Gall Bladder Related Adverse Events. The Clinical reviewer for the IBS-C indication discussed the findings of 20 patients who developed gall bladder related events during the placebo controlled and long term open label safety studies for the overall population for both the IBS-C and CIC trials. These included cholelithiases (13), gall bladder dyskinesia (5) and gallbladder cholesterolosis (2). The reviewers concluded, based on review of the literature, that the event rate was not increased over the background rate of the population. The Division of Epidemiology I of OSE was consulted to review literature that the applicant submitted to

[2] Strate LL, et al. Am J Gastroenterol online publication 10 July 2012. doi:10.1038/ajg.2012.194:
[3] Everhart JE, Ruhl CE. Gastroenterology 2009;136:741-54.

establish the expected background rate, and the consult reviewers concluded that the Italian Corazziari study "is the best source for a comparator incidence rate for gallstones in IBS patients." They noted that the estimates from that study are conservative because they established the gallstone-free group with ultrasound; therefore, the rates from the general US population study reports may be lower than that reported by Corazziari. In this light, they concluded the Linzess event rate is comparable to expected background rate.

Ischemic Colitis. The reviewers carefully evaluated the safety dataset for evidence of ischemic colitis. There were 3 cases of ischemic colitis reported in the clinical development program. One was diagnosed 11 days after stopping study drug (in a patient with CIC), and the other cases occurred during IBS-C open label long term safety trials. They noted that, based on the information available in the safety dataset, it is impossible to consider these 3 cases a signal for Linzess, since both IBS and constipation are independent risk factors for developing ischemic colitis. The reviewers explored the dataset for underreporting or lack of ascertainment by examining percentages of adverse event reports for various adverse event terms. The reviewer of the CIC trials identified 11 "cases of interest" that she believed should be further evaluated for ischemic colitis. She noted that there did not seem to be a temporal relationship between treatment initiation and time to developing the event in these cases. Five of the 11 were able to continue on treatment without recurrence, and for this reason she concluded that ischemic colitis was unlikely in these patients. The remaining 6 patients were sent for adjudication by the members of the applicant's Expert Panel. The Expert Panel concluded that there was insufficient evidence to conclude that these 6 patients' events represented ischemic colitis. The reviewers did not disagree with the panel's findings, based on their own review of the cases. The reviewers determined that the available evidence do not establish a causal link between Linzess and ischemic colitis. However, the Clinical reviewer of the CIC trials did state that this safety issue should be closely monitored in the postmarketing setting. She strongly advocated for inclusion of symptoms of ischemic colitis in the Medication Guide, with instructions to patients to contact their health care provider immediately should they develop. (b) (4)

Hematology. There was one patient in the CIC trials that developed aplastic anemia with pancytopenia. In light of this, I will present information on the hematology data from the phase 3 trials and long term safety studies. The patient with aplastic anemia was not taking drugs known to be associated with aplastic anemia, but did have an influenza-like illness at study start. The patient was Parvovirus B19 positive, indicating past exposure, but the reviewer stated that the aplastic anemia presentation in this patient was atypical for a case associated with parvovirus. The patient had a known diagnosis of hemachromatosis, however, the reviewer could find no evidence of an association between hemachromatosis and aplastic anemia. The reviewer noted that there are no reliable studies that have been conducted in the US population to document the incidence of aplastic anemia. The incidence in Europe and Israel is reported to be 0.6-3.1/million. The reviewer found that most cases of aplastic anemia are not associated with a drug or chemical (reported range = 3-27%; Young, et al, 2008c). A subgroup of the drugs associated with aplastic anemia have idiosyncratic reaction as a mechanism, whereas some of the drugs are outright cytotoxic and would be expected to cause bone marrow suppression.

The following table summarizing hematological data from the randomized, controlled trials (CIC and IBS-C) is reproduced from Dr. Dimick's Clinical Review. In the CIC placebo controlled trials, a very small percentage of patients developed absolute neutrophil count < 0.8 x LLN in both the placebo and Linzess arms, with a similar percentage among arms. In the IBS-C trials, patients in both placebo and Linzess arms experienced neutrophils that fell below 0.8 x LLN (normal is in range of 1500, so this is approximately <1200). The percentage was higher on the Linzess arm (2.2%), but the percentage was higher than observed in the 290 microgram Linzess arm (1.7%) of the CIC trials. The percentage of patients with neutropenia in placebo arms of the IBS-C trials was less than that reported in the placebo arms of the CIC trials. Examination of thrombocytopenia, at least as defined in the dataset (<0.5 x LLN), does not reveal a signal of thrombocytopenia associated with Linzess. Examination of red blood cell count, with low RBC defined as <0.9 x LLN, revealed a numerically higher percentage of patients with low RBC levels in the 290 microgram arms of the IBS and CIC trials (0.5%) compared to placebo and the lower dose arm (0.2% in both). There were no cases of low rbc counts in the placebo arm of the IBS-C trial. The meaningfulness of these low numbers is unclear. Examination of low Hct and Hgb revealed no clear difference among arms.

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

		CIC			IBS-C Patients	
Laboratory Parameter	PCS Criteria	Placebo n/N (%)	Linaclotide n/N (%)		Placebo n/N (%)	Linaclotide n/N (%)
			145 ug/day	290 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 × 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 × 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 × LLN	6/414 (1.4)	11/422 (2.6)	10/406 (2.5)	10/768 (1.3)	10/779 (1.3)
	> 1.5 × 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 × LLN	8/412 (1.9)	6/418 (1.4)	7/406 (1.7)	7/771 (0.9)	17/780 (2.2)
	> 1.5 × ULN	0/412	3/418 (0.7)	5/406 (1.2)	7/771 (0.9)	9/780 (1.2)
Platelet count	< 0.5 × LLN	0/419	1/421 (0.2)	0/409	1/773 (0.1)	0/780
	> 1.5 × ULN	0/419	1/421 (0.2)	0/409	3/773 (0.4)	2/780 (0.3)
Red blood cell count	< 0.9 × LLN	1/419 (0.2)	1/423 (0.2)	2/410 (0.5)	0/772	3/785 (0.4)
	> 1.1 × 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 × 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.

The IBS-C Clinical reviewer noted that for neutropenia, the data were inconsistent between the CIC and IBS-C populations, and the most marked difference from placebo was in IBS-C population. She noted that drops in neutrophil counts were transient in nature, and resolved by end of treatment. She also noted that many of the patients that shifted into the range of abnormal, were near abnormal at baseline. She acknowledged that there was a patient who was discontinued from treatment with linaclotide when their neutrophil count dropped from 1900 to 490 at the Day 85 visit. The platelet count also dropped to 147,000. This patient had borderline normal WBC and ANC at baseline. Drug was stopped 5 days after the Day 85 counts were documented. A repeat CBC a week after stopping drug revealed recovering WBC (2400), ANC (670) and platelet count (163,000). The patient reportedly had completely normalized by a followup evaluation on Day 110.

In the long term safety trials, neutropenia was reported in 2.2% of CIC patients and 2.0% of IBS-C patients. Low RBC counts were again noted: 1.2% in CIC patients and 0.3% in IBS-C patients. Low platelet counts were observed in only 2 patients in the long term safety trials. There were 9 patients in the open label long term safety studies that discontinued treatment due to a hematology-related treatment emergent adverse events. Five IBS-C patients discontinued due to anemia, 1 IBS-C patient for low WBC and neutrophil counts, 1 IBS-C patient due to low neutrophil count, low WBC count and low lymphocyte count, 1 IBS-C patient due to low platelet count and 1 CIC patient due to aplastic anemia. The latter patient was described above. I examined the other patients' narratives and serial CBC data. One patient who discontinued for anemia had mild anemia, normal ANC and platelet count, and was taking NSAIDs, which could have caused the anemia. There was a patient with a low baseline WBC (2.8) and ANC (1800) who demonstrated shifts back and forth between normal and abnormal range, and came off study when the fluctuations resulted in an WBC and ANC lower than baseline (WBC 2.5 and ANC 1100). The platelet count was unremarkable. An additional patient of interest had a baseline ANC of 2390, which dropped to 880. This patient's platelets were normal. After stopping the drug the ANC returned to normal.

Overall there was not a clear pattern of concern or signal for adverse hematological impact caused by Linzess. The product is poorly absorbed and any bone marrow effect presumably would have to occur via idiosyncratic reaction or immunological mechanism. For context, the lubiprostone NDA clinical review for the IBS-C indication was checked to determine the rates of neutropenia and anemia observed in those datasets. In the randomized controlled trials, shifts from normal to low WBC occurred in 5.7% placebo patients and 3% of lubiprostone 16 mcg treated subjects and 7% of lubiprostone 32 mcg treated subjects. Regarding hemoglobin, 1.7% of placebo subjects and 3% of lubiprostone 16 mcg subjects shifted from normal to low. The RBC count shifted from normal to low in 1.8% of placebo subjects vs. 3% of lubiprostone 16 mcg subjects. ANC shifted to low in 0.3% of placebo subjects and 1.8% of lubiprostone patients. These percentages are similar, if not higher, than those reported in the table above.

In the long term safety study of lubiprostone, which patients entered after completing a randomized withdrawal phase, the percentage of patients overall who shifted from normal to low WBC ranged 1-5%. The percentage shift to low ANC occurred in 1-5% of patients. RBC shifted to low in 1.8%-3.8% of patients, and hemoglobin declined in 1.8% to 5.7% of patients. These proportions of shifts are similar to that reported in this NDA and lubiprostone has not

been labeled with adverse events reflecting bone marrow failure, including in the Postmarketing Adverse events section.

Hypersensitivity. Adverse events suggestive of hypersensitivity occurred on both the Linzess and placebo arms. In the combined safety datasets for the four phase 3 trials, during the initial randomized, controlled treatment period, the rate of skin manifestations that might reflect underlying hypersensitivity (urticaria, pruritis, hives, erythematous rashes) was 1.3% for Linzess and 1.6% for placebo. In the same phase 3 trial dataset, potential pulmonary manifestations of hypersensitivity including terms such as dyspnea, wheezing, new onset asthma were reported in 0.7% of Linzess treated patients and 0.5% of placebo treated patients. Five cases of "hot flush" in the Linzess treated patients (and 1 placebo patient) in the randomized, controlled trials were not associated with rash or respiratory symptoms, so it is unlikely that these were cases of unrecognized anaphylaxis. In the long term safety trials (N=3270) there were 18 patients coded as having hypersensitivity adverse events (15 of which were urticaria), including one patient with anaphylaxis, which resolved with oral diphenhydramine and was not coded as an SAE. All but one of the patients with urticaria continued treatment without recurrence of the event.

The reviewers from Division of Therapeutic Proteins/Office of Biotechnology Products (DTP/OBP) were consulted regarding the need for further immunogenicity evaluation of Linzess. The OBP reviewers noted that although Linzess is a small peptide, it has multiple attributes that make it potentially immunogenic, including its 3 disulphide bonds, which render a more rigid tertiary structure than is typical for a 14 amino acid peptide. (b) (4)

Due to the structural homology of endogenous guanylin peptide family members, the OBP reviewer said the greatest risk, in terms of safety, if anti-Linzess antibodies were to develop, would be cross reaction with endogenous peptides that could lead to deficiency syndromes. For this reason, she recommended that the applicant should develop assays for IgM, IgA, and IgG anti-drug antibodies, and that patient samples should be tested for evidence of these antibodies.

The DGIEP reviewers examined the literature to develop an understanding of what the clinical manifestations of loss of guanylin peptide function might be, in order to establish that a signal for these events was not present in the safety data submitted in this NDA. Based on the review by Fonteles[4], the reviewers concluded that the likely adverse events associated with antibodies to guanylin would be hypernatremia, volume overload, hypertension, and constipation. A publication by Kulaksiz and Cetin[5] indicates that uroguanylin is present in the ductal epithelium of the pancreas and is involved in transfer of fluid into the pancreatic duct. The reviewers were unable to delineate a specific pancreatic manifestation of uroguanylin deficiency, but exocrine pancreatic insufficiency, as is seen in cystic fibrosis, is a hypothetical possibility. With regard to the latter, the reports of pancreatitis noted in Dr. Dimick's Clinical

[4] Fonteles MC and do Nascimento NRF. Can J Physiol. Pharmacol. 89:575-585 (2011).
[5] Kulasksiz H and Cetin Y. J of Endocrinology (2001) 170, 267-275.

review were re-examined in the context of this immunogenicity issue. One of the cases of pancreatitis occurred in a patient treated with placebo. The other occurred in a patient treated with Linzess in a long term safety study. This patient had a history of chronic pancreatitis. Therefore, the pancreatitis reported as an adverse event was unlikely to be secondary to an immune response to uroguanylin.

The NDA safety database was specifically examined for evidence of peripheral edema, pulmonary edema, fluid retention, hypertension, hypernatremia. Since all patients in these clinical trials had underlying constipation, and the applicant had presented group mean data that did not reveal a signal that antibodies were causing loss of response to treatment, the search terms did not include constipation. The searches included the entire ISS (comparing overall event percentages for Linzess and placebo) and a search that was narrowed to the concurrent placebo controlled portions of the 4 major trials, since presence of a concurrent control arm would allow the best ability to interpret the findings. These analyses did not reveal a signal suggesting endogenous protein deficiencies. The results of this exploration are summarized below.

No cases of hypernatremia were identified. Limiting the analyses to the four phase 3 trials dataset, during the initial placebo controlled treatment period, the rates of edema/fluid retention events (utilizing terms such as edema, fluid retention, extremity swelling, and excluding solitary joint swelling) were 1.4% in the Linzess arm patients (N=1657) and 1.2% in placebo arm patients (N=1218). In the overall safety dataset, the reviewers reported that the rate for combined terms of edema, swelling, fluid retention were 2.3% in Linzess treated patients vs. 3.2% in placebo patients. In the four phase 3 trials, during the initial treatment period, the rate of hypertension (combined search terms of hypertension and elevated blood pressure) was 1% in Linzess treated patients and 1.5% in placebo arm patients. In the overall safety dataset, the rate of hypertension plus elevated blood pressure was 1.6% for Linzess and 2.1% for placebo.

The Division worked with the OBP consultants and reviewers from Division of Biometrics 7 to delineate the features of the clinical trial that would provide patient samples for evaluating for presence of IgM, IgA and IgG anti-drug antibodies. The OBP consultants recommended a PMR trial in which patients were exposed to at least of year of drug, with samples obtained at 0, 2-weeks, 1, 3, 6 and 12 months. The applicant was contacted to determine whether they had archived samples from the clinical trials they had already conducted, and they stated that the archived samples were limited to a 4 week assessment. The OBP reviewers stated that a single sampling at 4 weeks was inadequate for this evaluation; however, the archived samples could provide information for sample size planning for the PMR trial, because these could indicate the proportion of positive samples that could be expected at 4 weeks in the planned trial. The absence of information on the specificity and sensitivity of the to-be-developed assays and absence of information on the proportion of patients who could be anticipated to develop antibodies made it difficult to prospectively identify the clinical trial sample size. This in turn made it difficult to determine an appropriate PMR target date for trial completion.

The reviewers discussed worse case scenarios, in terms of sample size, in which the goal was ruling out a specific event rate for a rare event (1/1000 or less), and found that without

adjusting for assay sensitivity and specificity of less than 100%, the sample size would be ≥1000. The team discussed relying upon the event rate in the NDA safety dataset for events specifically coded as hypersensitivity or urticaria to target the sample size, relying upon an assumption that all these events reflected manifestations of anti-drug antibodies. During that discussion the reviewers reported that there were approximately 24 events in patients treated with linaclotide in the combined double blind randomized, controlled trials and long term safety trial safety dataset (N=2971 linaclotide), which corresponds to an estimated predicted rate of anti-drug antibodies in the clinical trial of 0.8% and would necessitate a trial that enrolled approximately 400 patients, assuming the assay has 100% sensitivity and specificity. However, these reported adverse events may have had nothing to do with antidrug antibodies. If so, if actual development of antidrug antibodies is a rare event, a study size would in fact need to be in the thousands to prove that. (Narrowing the rate prediction to the one case that was specifically reported as anaphylaxis, the rate is 0.03%, 1/3270.)

These issues raised significant challenges in reaching an agreement on the milestone dates for the post-approval development of validated assays for anti-drug antibodies and completion of a clinical trial in which antibody titers would be assessed in patients receiving Linzess for one year. The OBP reviewers took a strong stance that the applicant should be able to develop validated assays within 18 months. The applicant stated that based on their consultations with experts, they had been advised that it would take longer. The applicant also proposed that it would take several years to complete the post-approval clinical trial, partly because they anticipated that it would take additional time to validate the assays, have them reviewed by the FDA, and then gain FDA's agreement that the assays were adequate for testing the archived 4 week samples (from completed trials) to help determine the sample size for the post-approval trial.

Although I agree with the OBP consultants that the trial to obtain samples can be initiated prior to FDA's completed review of the assay validation report, I am concerned that the clinical trials should not be initiated prior to there being adequate evidence that they applicant has been able to develop adequate assays. Should the FDA review the assay and find that it is not adequate for testing patient samples, I think it is difficult to justify enrolling substantial numbers of patients in a clinical trial for which there were inadequate data upon which to establish the ultimate target sample size. Moreover, if there is a high prevalence of anti-drug antibodies (found in the archived 4-week samples), enrollment of thousands of patients to obtain samples is difficult to justify. For this reason, I supported a protocol submission date that falls 5 months prior to the submission of the assay validation report. Based on the information available at that time, it may be possible to determine that enrollment can start shortly after protocol submission or that it should be further delayed. As long as the rate of enrollment is not brisk, it may be appropriate to enroll patients to begin obtaining samples during the completion of the FDA's review of the assay validation report and while the archived 4 week samples are being tested. Sample size and enrollment can be adjusted after this key foundational information is agreed upon (sensitivity and specificity) and further delineated (ascertainment of proportion of patients who have anti-drug antibodies in the 4 week samples). If ongoing enrollment is justified at that point (which it most likely will be), the trial can continue with interim analyses to reassess power assumptions and to monitor progress. The PMR clinical trial completion date of 4 years following submission of the assay

validation report (and 4 years plus 5 months after protocol submission), factors in the potential that the sample size of the trial may be thousands of patients, that patients will have to be followed for a year, and there may be delays in starting the trial related to development of a validated assay.

The following PMRs under FDAAA will be included in the Approval Letter.

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

Final Assay Validation Report: March 2014

1915-6 A clinical trial in adults receiving Linzess (linaclotide) to assess development of anti-drug antibody (ADA) responses in patient samples. Validated assays capable of sensitively detecting ADA responses that may be present at the time of patient sampling, developed under PMR 1915-4 above, will be used. Sampling will occur at 0 and 2 weeks, and at 1, 3, 6 and 12 months. Immunogenicity rates and individual patient titers will be evaluated. Adverse events will be collected.

Final Protocol Submission: November 2013
Trial Completion: March 2018
Final Report Submission: December 2018

Dose Adjustment. Although only one dose level of Linzess was studied for the IBS-C indication, approximately 20% of patients on the 290 microgram dose had their dose reduced to 145 micrograms in the long term safety study. Some patients whose doses were reduced subsequently underwent a readjustment back up to the original dose. The most common adverse event that led to dose adjustment was diarrhea. The review team discussed whether product labeling for the IBS-C indication should include instructions for dose reduction to the 145 microgram dose level, even though the efficacy of that dose was not studied in IBS-C. In light of the absence of robust efficacy data for that dose level in IBS-C, and evidence that some patients returned to the higher dose after initial reduction, the team concluded that there was inadequate evidence to support instructions for dose reduction. The lower dose will be available and health care providers may try this strategy, but inclusion of label instructions to do so could suggest that evidence exists establishing 145 micrograms as an effective dose level in IBS-C.

The Statistical reviewer has suggested in his review that the lower dose level should be considered for efficacy testing in IBS-C in the future. He observed that the efficacy of Linzess in treatment of IBS-C was modest, but suggested that in light of the similar efficacy between the two dose levels tested in CIC, the lower dose may be as effective as the higher dose in

IBS-C (b) (4). The lower dose may be better tolerated from the standpoint of diarrhea. In light of the availability of the lower dose for exploration of dose reduction as needed, the Clinical reviewers did not ask for a PMC to establish the efficacy of the lower dose in IBS-C. I concurred with the Clinical reviewers. The sponsor conducted dose finding phase 2 trials to identify the dose studied in IBS-C. IBS-C is not the same condition as CIC, and has a significant pain component. Therefore, there is reason to believe that the findings from the CIC trials are not generalizable to IBS-C, in terms of optimal dose for efficacy.

9. Advisory Committee Meeting

There was no Advisory Committee convened to discuss this application because the clinical trial design was acceptable and the application did not raise questions that necessitated seeking input from outside expertise. .

10. Pediatrics

(b) (4) . In light of the findings in the neonatal/juvenile mouse studies, the reviewers met with members of the Pediatric and Maternal Health staff, including the Associate Director, to discuss their concerns about the need for further nonclinical data to delineate the mechanism of death in the neonatal/juvenile mice before embarking on pediatric trials. During those meetings pediatric labeling was also discussed. Ultimately, consensus was reached that a nonclinical study in neonatal and juvenile mice to determine the mechanism of death should be a required pediatric study under 505B(a) of the Federal Food, Drug, and Cosmetic Act, and that the deferred pediatric studies for CIC in children 7 months to 17 years and for IBS-C in children 7 years to 17 years should be delayed until the completion of the nonclinical study. The pediatric study requirement for CIC in ages birth to 6 months and irritable bowl syndrome in ages birth to 6 years will be waived because the studies are impossible or highly impracticable, due to there being too few children with this condition to study.

The following deferred pediatric studies will be required:

1915-1 A nonclinical study in neonatal and juvenile mice to determine the mechanism of death in neonatal and juvenile mice treated with linaclotide.

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

1915-2 A safety and efficacy study in pediatric patients with chronic idiopathic constipation ages seven months to 17 years.

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

1915-3 A safety and efficacy study in pediatric patients with irritable bowel syndrome with constipation ages seven years to 17 years.

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

With regard to pediatric labeling, the group initially reached consensus that the labeling should carry a contraindication for the entire age range. During that discussion the Associate Director of PMHS clarified that a contraindication would not preclude PREA study requirements in a situation in which additional nonclinical data are needed to determine whether or not pediatric studies can proceed and in which age groups. The Associate Director agreed that once the nonclinical data are reviewed, the applicant can be released from the requirement if the data indicate that the studies should not be performed for safety reasons. If the nonclinical data support removing the contraindication entirely, or for a specific age range, then the human pediatric studies for which safe dosing has been supported, can proceed.

Subsequent to that meeting there were discussions with the applicant and internal discussions regarding the necessity of an absolute contraindication for the entire age range, i.e., including the older pediatric age groups in the Contraindication. In light of the fact that the neonatal/juvenile mice data were most directly applicable to the youngest pediatric age group, the review team found it difficult to justify an absolute contraindication in older children. Extension of the contraindication to the full age range was not based on the existence of nonclinical safety data that were directly applicable to older children, but had been proposed to discourage off label use until there was a better understanding of the mechanism of lethality, which could then help define which specific age groups can safely take Linzess. The reviewers agreed that a boxed warning to avoid administration of Linzess to older children based on lethality observed in neonatal/juvenile mice could prevent off label administration of the product in older children. The human age for which the mouse data most strongly provide evidence against exposure is 2 years and less. The Contraindication was extended up to 6 years to provide a margin of safety. The Boxed Warning will state use in children 6 through 17 years should be avoided. The review staff is committed to changing the Boxed Warning and Contraindication, as appropriate, once the data from future mouse studies have been reviewed and have established that it is appropriate to change the label and initiate pediatric clinical trials.

Section 8.4 Pediatric Use of the label will restate the contraindication and warning, and will provide the nonclinical information upon which this guidance is based.

As discussed in Section 5 Clinical Pharmacology, the Clinical Pharmacology reviewers recommended a postmarketing clinical trial to establish whether Linzess or its active metabolite is present in breast milk of nursing mothers. Even though linaclotide and its metabolite are not detectable in patients treated at the doses labeled, they stated that without actual testing for levels in breast milk, we cannot exclude that Linzess is transported into and concentrated in breast milk. These recommendations were discussed with the Pediatric and Maternal Health staff (PMHS) consultants, who fully supported the recommendation for this

trial to be conducted as a PMR under FDAAA. The following PMR clinical trial under FDAAA will be included in the approval letter:

1915-5 A multiple-dose milk-only lactation trial in healthy lactating but non-nursing female volunteers receiving Linzess (linaclotide) to assess concentrations of linaclotide and its active metabolite in breast milk, using a validated assay in order to appropriately inform the nursing mothers' subsection of the labeling.

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

The implications of the PMR clinical trial for the product labeling for nursing mothers were re-discussed with the PMHS team. They firmly stated that the scientific basis for conducting this study as a PMR should have no impact on Section 8.3 Nursing mothers. The available data do not establish a risk/benefit assessment that nursing mothers should be instructed that they cannot take Linzess when nursing their infant. The label will state that caution should be exercised when Linzess is administered to a nursing mother, and will include references to the Contraindication, Warnings and Precautions, Section 8.4 Pediatric Use and Clinical Pharmacology to help health care providers make appropriate risk/benefit decisions for their patients who are nursing.

11. Other Relevant Regulatory Issues

Six clinical sites were inspected by DSI. These sites were involved in both the CIC and IBS-C phase 3 trials. The IND sponsor was also inspected for data collection, handling and archiving. The DSI review concluded the data appear adequate to be used in support of the NDA. The clinical trial site deviations were determined to not have a substantial effect on final safety and efficacy evaluations.

Please refer to the Clinical Reviews for financial disclosure information. The financial disclosure process and review was complicated by the fact that there were two partners involved in the clinical development, Ironwood Pharmaceuticals, Inc and Forest Laboratories, Inc. As stated in Dr. Wynn's review, "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….. 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…..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."

There were investigators who received speaker payments, consulting and writing service payments. The specific reimbursements received are listed in Dr. Dimick's clinical review. The spouse of one subinvestigator was an employee of Forrest Laboratories.

The Clinical reviewers concluded that the applicant's assertions than any financial arrangements between clinical investigator and the sponsors were minimized by the study design elements of the major phase 3 trials submitted in support of this application were reasonable. I agree.

12. Labeling

See other sections of this review (in particular Section 10 Pediatrics, Section 7 Efficacy and Section 8 Safety) and the CDTL review for labeling review issues and recommendations.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Approval
- Risk Benefit Assessment – All review disciplines have recommended approval. I agree that the risk benefit profile of Linzess, as described by the adequate and well, controlled trials submitted in support of this applicant, is favorable, and that the product should be approved for treatment of chronic idiopathic constipation and treatment of IBS-C. The safety review did not identify safety issues that preclude approval. The concerns raised by the neonatal/juvenile mouse study have been addressed through product labeling, with a Contraindication and a Boxed Warning. An additional neonatal/juvenile mouse study will be conducted as a PMR under PREA to more clearly define the mechanism of neonatal lethality. In the future, the product label can be modified, as appropriate, based on a better understanding of the risk of exposure of all pediatric age groups derived from the nonclinical study. Once it has been established that it is safe to embark on pediatric human studies, the product label will be modified.

  Linzess is a peptide that may result in development of anti-drug antibodies that could theoretically cross react with endogenous guanylin proteins, resulting in clinical deficiency syndromes. There was no evidence of a signal of clinical deficiency syndromes identified in the clinical safety dataset submitted in this application. There were patients who developed evidence of hypersensitivity; however, these events occurred in both the linaclotide and placebo arms of the randomized trials. The applicant will be required to develop validated assays for antidrug antibodies and will be required to test patient samples for the presence of these antibodies. The samples will be prospectively collected over a 1 year period of drug exposure in a clinical trial, and adverse events will be collected to support examination of relationships between the presence of antibodies and adverse events.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

The reviewers have not recommended a REMS and I concur.

- Recommendation for other Postmarketing Requirements and Commitments

Human pediatric trials required under PREA will be delayed until a nonclinical study in neonatal and juvenile mice to determine the mechanism of death in neonatal and juvenile mice treated with linaclotide has been conducted and reviewed. This nonclinical study is a required study under PREA. (See Section 10 Pediatrics of this review and the approval letter.).

There will be a PMR clinical trial under FDAAA for ascertaining levels of linaclotide and its metabolite in breast milk. (See Section 10 Pediatrics and the approval letter.)

There will be a PMR study and PMR clinical trial, each required under FDAAA, to evaluate immunogenicity. (See Section 8 Safety and the approval letter.)

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/s/

DONNA J GRIEBEL
08/29/2012