CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206940Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	(electronic stamp)
From	Donna J. Griebel, MD
Subject	Division Director Summary Review
NDA	206940
Applicant Name	Furiex Pharmaceuticals, Inc
Date of Submission	June 26, 2014 Received June 27, 2014
PDUFA Goal Date	May 27, 2015
Proprietary Name / Established (USAN) Name	eluxadoline
Dosage Forms / Strength	Oral tablets/ 100 mg and 75 mg
Proposed Indication	Treatment of Irritable Bowel Syndrome with Diarrhea (IBS-d)
Recommended Action for NME:	*Approval*

Material Reviewed/Consulted	**Names of discipline reviewers**
Medical Officer Review	Laurie Muldowney, MD/Ruyi He, MD
Statistical Review	Yeh-Fong Chen, PhD/Mike Welch, PhD
Pharmacology Toxicology Review	Tamal Chakraborti, PhD/Sushanta Chakder
CMC/Biopharmaceutics Review	Yichun Sun, PhD/Assadollah Noory, PhD/TienMien Chen, PhD/ Paul Seo, PhD
Clinical Pharmacology Review	Dilara Jappar, PhD/Sue Chih Lee, PhD
OPDP	Adewale Adeleye, PharmD, MBA/Kathleen Klemm, PharmD
DMPP	Karen Dowdy, RN, BSN /Shawna Hutchins, MPH, BSN/RN/LaShawn Griffiths, MSHS-PH, BSN, RN
DGCPC/OSI	Susan Leibenhaut, MD/Susan D. Thompson,MD/Kassa Ayalew, MD, MPH
CDTL Review	Ruyi He, MD
OSE/DMEPA	Sherly Abraham, RPh/Kendra Worthy, PharmD/Lubna Merchant, MS, PharmD
OSE/DRISK	Nyedra W. Booker, Pharm.D., M.P.H./Jamie Wilkins-Parker, Pharm.D./Reema Mehta, PharmD, MPH
Division of Pediatric and Maternal Health	Carol H. Kasten, MD/Tamara Johnson, MD, MS/Ethan Hausman, MD/Lynne P. Yao, MD
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OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion=
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DGCPC=Division of Good Clinical Practice Compliance
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
DMPP=Division of Medical Policy Programs
CDTL=Cross-Discipline Team Leader

Division Director Review

1. Introduction

The applicant proposes marketing eluxadoline, a new molecular entity, for treatment of diarrhea-predominant Irritable Bowel Syndrome (IBS-d). Eluxadoline is a mu opioid receptor agonist, delta opioid receptor antagonist and kappa opioid agonist. Given the low oral bioavailability, the applicant proposes the therapeutic effects occur via local effects on opioid receptors within the GI tract. Two randomized, placebo-controlled trials support the NDA. The major review issues were related to safety, and my review will focus mainly on those issues.

The applicant identified cases of pain attributed to sphincter of Oddi spasm. Patients with a history of cholecystectomy were at higher risk for this adverse reaction. In patients with a history of cholecystectomy, the proportion of patients with abdominal pain due to sphincter of Oddi spasm increased with increasing eluxadoline dose. Based on these findings, the review team recommended that the product labeling include two dose levels (75 mg and 100 mg), and that the lower dose should be recommended for patients without a gall bladder. In addition, based on the review of the clinical pharmacology data submitted in the NDA, the lower dose will be recommended for patients who will have higher exposures to eluxadoline, i.e., patients with mild or moderate hepatic impairment (Child-Pugh Class A or B) and patients receiving concomitant OATP1B1 inhibitors. The reviewers also concluded that given the evidence of efficacy associated with the 75 mg dose level, the label could include instructions to dose reduce to 75 mg in patients having difficulty tolerating 100 mg.

In addition, given the recent safety PMR observational studies required as a basis for the Division of Gastroenterology and Inborn Errors Products' approval of the opioid antagonists methylnaltrexone and naloxegol, the review team considered whether the approval letter for the eluxadoline NDA should include a similar PMR study as a condition of approval, given that eluxadoline is a delta opioid antagonist.

Finally, the Controlled Substance Staff reviewed the applicant's nonclinical and clinical data submitted in support of its proposed Eight Factor Analysis, to determine what Schedule FDA would recommend to HHS and DEA for this new product. These issues will be discussed in Sections 8 Safety and 11 Other Relevant Regulatory Issues of my review.

2. Background

The diagnostic criteria for diarrhea-predominant Irritable Bowel Syndrome (IBS-d), as defined by Rome III criteria, include:

> Recurrent abdominal pain or discomfort ("an uncomfortable sensation not described as pain"[1]) at least 3 days per month in the last 3 months associated with 2 or more of the following:
>
> a. Improvement of pain with defecation
> b. Onset of pain associated with a change in frequency of stool
> c. Onset associated with a change stool form (consistency/diarrhea)

Alosetron, a serotonin 5-HT3 receptor antagonist, is the only drug approved and currently marketed for diarrhea-predominant Irritable Bowel Syndrome (IBS-d). It was temporarily

[1] Appendix A Rome III Diagnostic Criteria for Functional Gastrointestinal Disorders

withdrawn from the market in 2000 due to adverse reactions including ischemic colitis, severe constipation and death. It was subsequently reintroduced to the market with a Risk Evaluation and Mitigation Strategy (REMS) and with a limitation of use to patients with severe symptoms in whom the benefit outweighs the risk. It is now approved only for women with "severe" IBS-d symptoms for greater than 6 months who have not responded adequately to "conventional therapy" and who have "no anatomic or biochemical abnormalities of the GI tract". "Severe" IBS-d is defined in the alosetron label as diarrhea with one or more of the following: frequent and severe abdominal pain/discomfort, frequent bowel urgency or fecal incontinence, disability or restriction of daily activities due to IBS. The REMS goals are: 1) To mitigate the risk of ischemic colitis and serious complication of constipation associated with alosetron by ensuring that it is used in only severely affected patients for whom benefits exceed the risks, and 2) to ensure that the risk of ischemic colitis and serious complications of constipation with the use of alosetron are communicated to patients, pharmacists, and prescribers. Ischemic colitis was reported in both clinical trials and in post marketing use.

To provide some context for review of the adverse event profile associated with eluxadoline (as presented in the Safety section of this review and the Clinical reviews), I will briefly summarize the safety information found in the alosetron label regarding rates of constipation and GI complications reported in the clinical trials data base. There were 22 repeat-dose studies of patients with IBS treated with a dose of alosetron 1 mg twice daily (the approved dose is 0.5 mg twice daily, with escalation to 1 mg twice daily if the 0.5 mg dose is tolerated), which exposed 8,328 patients to alosetron and 2363 to placebo. Constipation was reported in approximately 29% of patients treated with alosetron 1 mg twice daily, and 11% of the patients treated at this dose withdrew from the studies due to constipation. At the 0.5 mg twice daily dose level (at which only 243 patients were exposed in the IBS trials), 11% reported constipation and 4% withdrew from studies due to constipation. In the IBS alosetron clinical trials, the cumulative incidence of ischemic colitis was 0.2% (2 per 1000 patients, 95% confidence interval 1 to 3) through 3 months and was 0.3% (3 per 1000 patients, 95% confidence interval 1 to 4) through 6 months. Serious complications of constipation, including obstruction, ileus, impaction, toxic megacolon, and secondary bowel ischemia, were also reported with use of alosetron during clinical trials. The incidence of serious complications of constipation was approximately 0.1% (1 per 1000 patients).

The rate of constipation and discontinuation due to constipation was lower in the eluxadoline safety dataset. For comparison, the eluxadoline label reports that 8% of the 1032 patients treated at the 100 mg dose level had constipation (compared to 3% of placebo), and 7% had an adverse reaction of abdominal pain (compared to 4% of placebo arm patients). Rates of severe constipation were less than 1% in patients receiving 75 mg and 100 mg eluxadoline. The most common reasons for discontinuation due to adverse reactions were constipation (1% for 75 mg and 2% for 100 mg) and abdominal pain (1% for both 75 mg and 100 mg). In comparison, less than 1% of patients in the placebo group withdrew due to constipation or abdominal pain. See Section XX Safety of my review regarding ischemic colitis and obstruction events in the eluxadoline program.

Loperamide, a mu opioid rector agonist, is a commonly used antidiarrheal medicine currently marketed in the U.S. It is not specifically indicated for IBS-d. It was approved in the United States as a prescription treatment for diarrhea in 1976. In 1988, it was approved for over-the-counter treatment of diarrhea. Loperamide is used to reduce diarrhea in patients with IBS-D.[2]

[2] Viera AJ, Hoag S, and Shaughnessy J. Am Fam Physician. 2002 Nov 15;66(10):1867-1875,

Regulatory History. The IND was submitted in November 2007 and was granted fast track designation in January 2011. The applicant and the FDA met multiple times during the course of drug development to reach agreement on general study design issues, including the primary efficacy endpoint. The duration of the randomized, controlled efficacy evaluation extended to 26 weeks to meet EMA's recommendation, and there was an efficacy analysis at 12 weeks, to be consistent with FDA guidance.

The primary endpoint of the trial was consistent with the FDA's Guidance for Industry: Irritable Bowel Syndrome – Clinical Evaluation of Drugs for Treatment. The FDA's IBS Guidance, which was posted as a draft guidance in March 2010, was finalized in May 2012. The Guidance recommends a treatment period of at least 8 weeks duration, followed by a randomized withdrawal design to address the need for maintenance treatment to prevent recurrence of signs and symptoms of IBS. The Guidance recommends a primary endpoint that measures the effect of treatment on two major IBS signs and symptoms: abnormal defecation and abdominal pain, and the primary efficacy analysis should compare response rates between the investigational drug and placebo. For IBS-D, the Guidance recommends that the defecation component be evaluated by assessing stool consistency with the Bristol Stool Form Scale. (Stool frequency should be evaluated as a key secondary endpoint, using weekly number of bowel movements.) For IBS-D, the Guidance recommends a responder definition as a "weekly responder" or a "daily responder" in which the individual patient is a weekly responder in both pain intensity and stool consistency (a composite endpoint), as follows:

1) Abdominal Pain Intensity Weekly Responder = patient experiences at least a 30% decrease from baseline in weekly average of worst abdominal pain score in the past 24 hours
2) Stool Consistency Weekly Responder = patient experiences at least a 50% reduction in the number of days per week with at least one stool that has a consistency of Type 6 or 7, compared to baseline. (Type 6 on the Bristol Stool Form Scale is described as "fluffy pieces with ragged edges, a mush stool" and Type 7 is "watery, no solid pieces. Entirely Liquid")

The Guidance states that a patient is a "daily responder" if the patient responds in both pain intensity and stool consistency in the evaluated 24 hour period (at least 30% reduction of pain relative to baseline and stool consistency is *less than* Type 5 for all bowel movements on that day (Bristol Stool Scale descriptor language: Type 5 = "soft blobs with clear-cut edges, passes easily" and Type 4, which is the highest score that would be considered responder consistency, = "Like a sausage or snake, smooth and soft").

The Guidance recommends the following pain severity and stool consistency for IBS-D trial eligibility:

1) Abdominal Pain Intensity: weekly average of worst daily (in past 24 hours) abdominal pain score of ≥ 3.0 on a 0 to 10 point scale , and
   Stool Consistency: at least one stool with a consistency of Type 6 or Type 7 Bristol Stool Score on at least 2 days per week. (Type 6 = "fluffy pieces with ragged edges, a mushy stool"; Type 7 = "Water, no solid pieces, entirely liquid")

3. CMC/Biopharmaceutics

I concur with the conclusions reached by the chemistry reviewer that the NDA has provided sufficient information to assure identity, strength, purity and quality of the drug product. The Biopharmaceutics reviewers have recommended the following PMC, which will be included in the approval letter:

2901-9 Conduct a study of the product dissolution and acceptance criterion to assess post-approval product quality using the following:

- Re-evaluate the dissolution acceptance criterion based on the dissolution data collected from at least 10 batches of commercial drug products (5 batches of 75 mg and 5 batches of 100 mg), manufactured over a maximum period of 1 year post-launch.

- Add a 15- minute time-point to the dissolution test at time of product release and in the stability protocol where profiles will be followed at 10, 15, 20, 30, 45, and 60 minutes.

- Assess the dissolution criterion of Q= (b) (4)% at 10, 15, or 20- minute time points and submit the newly proposed dissolution criterion with supportive dissolution profile data to the Agency for review.

Timetable:

Completion of dissolution data assessment: Launch date + 12 months
Submission of dissolution data assessment: Launch date + 14 months

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewers have recommended approval of this NDA. They found no nonclinical issues that would preclude approval. I concur. The following summary is reproduced from the nonclinical review:

> "Chronic oral toxicology studies were conducted in rats (6-month) and monkeys (9-month) to support chronic use of eluxadoline. The no-observed-adverse-effect-levels (NOAELs) in rats and monkeys were 2000 and 200 mg/kg/day, respectively (about 11 and 14 times, respectively, the human AUC of 24 ng.h/mL after a single oral dose of 100 mg). In a 4-week oral toxicology study in juvenile rats, the NOAEL was 1500 mg/kg/day.
>
> Eluxadoline was negative in the Ames test, chromosome aberration assay in human lymphocytes, the mouse lymphoma cell (L5178Y/TK$^{+/-}$) forward mutation test and the in vivo rat bone marrow micronucleus test. Oral administration of eluxadoline for 104 weeks did not produce tumors in mice and rats at up to 14 and 36 times, respectively, the human AUC of 24 ng.h/mL after a single oral dose of 100 mg.
>
> Eluxadoline at oral doses up to 1000 mg/kg/day (about 10 times the human AUC of 24 ng.h/mL after a single oral dose of 100 mg) was found to have no adverse effect on fertility and reproductive performance of male and female rats. Embryofetal development studies in rats and rabbits at oral/SC doses up to 1000/5 mg/kg/day (about 51 and 115 times, respectively, the human AUC after a single oral dose of 100 mg) did not cause any adverse effects on embryofetal development. A pre and postnatal development study in rats showed no evidence of any adverse effect on pre and postnatal development at oral doses of eluxadoline up to 1000 mg/kg/day (about 10 times the human AUC after a single oral dose of 100 mg)."

The nonclinical reviewer noted impurity (b) (4) (b) (4) was present at higher than ICH reportable levels, requiring ICH Q3A identification and qualification thresholds. The reviewer found the applicant's proposed specification for this impurity acceptable. The nonclinical data cited to support the specification were based on the amount of the impurity

weight/weight of the product administered in the toxicology, reproductive toxicology and carcinogenicity studies submitted in the NDA to support the safety of eluxadoline.

There were 3 residual organic solvents identified in the drug substance that are not listed in the ICH Q3C document: (b) (4) The reviewers found the applicant's proposed limits for these solvents acceptable. For (b) (4), the proposed specification of NMT (b) (4) ppm was acceptable in part based on a theoretical calculation of safety margin based on a rat study reported in the Material Safety Data Sheet submitted by the applicant. That rat study reported an oral LD50 that ranged from (b) (4) mg/kg. The reviewers calculated a safe dose for humans from that study based on a 100 fold safety factor and assuming a 50 kg body weight. The result was a human dose of (b) (4) mg/day, which is (b) (4) times higher than the human exposure to (b) (4) at the proposed specification, based on a 100 mg BID eluxadoline dose, which was (b) (4) mg/day. The reviewers noted also that this solvent is not listed as a carcinogen in a number of common references. Regarding (b) (4), the proposed specifications were well within the PDEs calculated based on nonclinical information. For (b) (4), the proposed specification for eluxadoline is approximately (b) (4) times less than the safe human exposure based on the PDE. For (b) (4), the proposed eluxadoline specification is (b) (4) times less than the PDE.

5. Clinical Pharmacology

I concur with the conclusions reached by the Clinical Pharmacology reviewers that there are no outstanding clinical pharmacology issues that preclude approval. I concur with their final labeling recommendations. I also concur with their recommendation for a PMR renal impairment study and with their recommendations for a number of PMCs, which are described below.

Pharmacokinetics. After single dose administration of eluxadoline 100 mg in healthy subjects, the peak plasma concentration was reached at ≈ 2 hours. C_{max} was approximately 2-4 ng/mL. A dose proportional increase in C_{max} and slightly less than dose proportional increase in AUC was observed. PK variability was high (51-98%). Eluxadoline exposure was 35 % higher in females than in males. Administration with a high fat meal decreased C_{max} by 50% and AUC by 60%. The product label will recommend taking eluxadoline with food since it was administered with food in the phase 3 trials that support its efficacy and safety. The terminal half-life of eluxadoline across phase 1 studies ranged 3.7-6.0 hr. In the mass balance study, about 0.12% and 82% of the administered radioactive dose was recovered in urine and feces, respectively.

Limitations of the data submitted to support describing eluxadoline's human metabolism led the reviewers to conclude that "it is unknown if eluxadoline is a substrate for CYP enzymes." The bioanalytical methods used in the metabolic profiling studies to monitor the metabolites in plasma and urine did not have adequate assay sensitivity. In addition, the *in vitro* test systems for various phase 1 and 2 enzymes were not adequately verified prior to study. In the *in vitro* human pooled hepatocyte study, the positive control was limited to a CYP2C9 substrate . In the human microsome and S9 study, the positive control was limited to midazolam (which only measures CPY3A4 activity), and the data for the positive and negative controls were not provided for evaluation. Therefore, the potential that there is metabolism mediated via other enzymes couldn't be ruled out. Based on these deficits, the reviewers recommended the following PMC, which will be included in the approval letter:

2901-5 Conduct an *in vitro* study to determine the specific isozymes involved in the metabolism of eluxadoline.

Final Protocol Submission: 01/01/2016
Study Completion: 12/31/2016
Final Report Submission: 03/31/2017

In addition, the reviewers recommended that Section 12.3 Pharmacokinetics of product labeling state the following information under the subheading "Metabolism": "Metabolism of eluxadoline is not clearly established *[see Drug Interactions (7)]*." Section 7 Drug Interactions will include the following general reference to use with "strong CYP Inhibitors" as a precautionary measure, since it is currently unknown whether eluxadoline's metabolism is impacted by CYP inhibitors and increased exposure could have an impact on safety related to CNS effects.

Strong CYP Inhibitors*	
Clinical Impact:	Potential for increased exposure to eluxadoline *[see Clinical Pharmacology (12.3)]*
Intervention:	Monitor patients for impaired mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery and for other eluxadoline-related adverse reactions *[see Adverse Reactions (6.1)]*.
Examples:	ciprofloxacin, (CYP1A2), gemfibrozil (CYP2C8), fluconazole, (CYP2C19), clarithromycin (CYP3A4), paroxetine and bupropion, (CYP2D6)

*As a precautionary measure due to incomplete information on the metabolism of eluxadoline

Hepatic Impairment. The applicant conducted a hepatic impairment study and found that eluxadoline plasma concentrations (both AUC and C_{max}) increased 6 fold in patients with mild (Child-Pugh Class A) hepatic impairment and 4 fold in patients with moderate (Child-Pugh Class B) impairment relative to exposure in subjects with normal hepatic function. In patients with severe (Child-Pugh Class C) impairment, the AUC and C_{max} increased 16-fold and 19-fold, respectively. The applicant proposed a contraindication in patients with hepatic impairment; however, the Clinical pharmacology reviewers recommended that the contraindication should be limited to patients with severe impairment. In discussions with the Clinical team, the reviewers pointed out that it was not clear what adverse reaction related to even 20 fold increase in systemic exposure would warrant contraindicating its use, even in the severe impairment population. However, patients with severe hepatic impairment can have mental status changes from their disease, and the increased exposure could have CNS effects that could further complicate the patient's mental status. After discussion with the Clinical team, there was agreement that a contraindication in the setting of severe hepatic impairment could be justified. The applicant agreed to limit the contraindication to patients with severe impairment. For patients with mild or moderate hepatic impairment, the label will state, in Section 8.6 Hepatic Impairment:

> "In patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment…..Administer VIBERZI at a reduced dose of 75 mg twice daily to these patients *[see Dosage and Administration (2)]*. Monitor patients with any degree of hepatic impairment for impaired mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery and for other eluxadoline-related adverse reactions *[see Adverse Reactions (6.1)]*."

Renal Impairment. The applicant did not conduct a dedicated renal impairment PK study. The reviewers examined adverse event data from the phase 3 trials in subjects who had evidence of renal impairment. In patients with mild impairment, the percentage of adverse events was similar to the overall study population. There were only 6 patients

with moderate renal impairment, which was inadequate for assessment. The Clinical Pharmacology reviewers recommended that the approval letter include a PMR to study pharmacokinetics of eluxadoline and characterize the risk of CNS adverse reactions in patients with renal impairment. I concur. The letter will state:

> "Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.
>
> We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of euphoria and other CNS adverse effects based on increased drug concentrations in patients with renal insufficiency.
>
> Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.
>
> Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:
>
> 2901-4 A dedicated clinical pharmacology trial to evaluate the impact of renal impairment on eluxadoline pharmacokinetics and the risk for euphoria and other CNS adverse effects.
>
> The timetable you submitted on May 7, 2015, states that you will conduct this trial according to the following schedule:
>
> Final Protocol Submission: 01/01/2016
> Trial Completion: 12/31/2017
> Final Report Submission: 06/30/2018"

Drug-Drug Interaction Evaluation. When determining the appropriate content for Section 7 Drug Interaction of the product label, the reviewers considered potentially clinically relevant differences in eluxadoline's impact on CYP enzymes and transporters if the interaction occurred via systemic vs. local exposure within the gut lumen (which would impact drug levels of other drugs that are CYP substrates or subject to transport via these transporters). Eluxadoline concentrations tested *in vitro* were relevant for systemic exposure interactions; however, may have been too low for evaluating local interactions at the gut lumen level. This was particularly relevant for CYP 3A4 and the transporters BRCP and P-gp, in light of their known presence/function in the gut.

Cyp Induction: The applicant submitted *in vitro* data that indicated that eluxadoline does not induce CYP1A2, CY2C9, CYP2C19 and CY3A4/5.

CYP Inhibition: The applicant submitted an *in-vitro* study (human microsomal liver suspension with and without NADPH) that evaluated eluxadoline's potential for time dependent CYP-inhibition, which would impact other drugs that are CYP substrates. Primary incubations were 60 minutes in duration. This study revealed eluxadoline inhibited CYP3A4 activity in a concentration and NADPH dependent manner. According to the reviewers, these data "suggested a potential for mechanism-based inhibition of CYP3A4". (*In vitro* study did not show time dependent inhibition of CYP1A2, 2C9, 2C19 and 2D6.) The *in vivo* relevance of the interactions observed in this study could not be assessed because the applicant did not calculate the R2 value, due to lack of data to compute the Ki and Kinact values (apparent inactivation constant and maximal inactivation rate constant, respectively) needed for the calculation. The R2 value is needed to assess the relevance of the observed mechanism based inhibitory interaction, and there was no *in vivo* study conducted to evaluate CYP3A4 interaction. The reviewers

concluded that further *in vitro* study is needed to better describe the potential for eluxadoline to inhibit CYP3A4. If the additional *in vitro* data suggest there is relevant inhibition, a subsequent in vivo assessment will be needed to assess whether eluxadoline causes clinically relevant CYP3A4 inhibition, in particular at the gut level. They recommended the following PMC to address this issue, which will be included in the approval letter:

2901-6 Conduct an *in vitro* study to assess the time-dependent inhibition of CYP3A4 by eluxadoline.

Final Protocol Submission: 01/01/2016
Study Completion: 12/31/2016
Final Report Submission: 03/31/2017

In the meantime, the Clinical Pharmacology review recommended that the label state "monitor the systemic level of narrow therapeutic index drugs that are CYP3A4 substrates when concomitant use with eluxadoline is initiated or discontinued". The label will contain a table that includes the following information to address this recommendation:

CYP3A Substrates with Narrow Therapeutic Index	
Clinical Impact:	Potential for increased exposure of co-administered drug *[see Clinical Pharmacology (12.3)]*
Intervention:	Monitor drug concentrations or other pharmacodynamic markers of drug effect when concomitant use with eluxadoline is initiated or discontinued.
Examples:	alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus

Furthermore, because the applicant did not conduct in vitro studies to evaluate the potential for eluxadoline to inhibit CYP2C8 or to induce CYP2B6, the reviewers recommended PMCs to address these gaps. The following will be included in the approval letter:

2901-8 Conduct an *in vitro* study to evaluate the potential of eluxadoline to inhibit CYP2C8 and induce CYP2B6.

Final Protocol Submission: 01/01/2016
Study Completion: 12/31/2016
Final Report Submission: 03/31/2017

(As stated above, the metabolism of eluxadoline has not been clearly established. The impact of drugs that are CYP inhibitors on eluxadoline levels has not been characterized. For this reason, as described earlier, the label will state that there is a potential for increased eluxadoline exposure with concomitant use with strong CYP inhibitors.)

Transporters: With regard to transporters, upon completion of their review the reviewers recommended the following for inclusion in Section 12.3 of the label (under sub header Drug Interactions):

> *In vitro* studies suggest that eluxadoline is a substrate for OAT3, OATP1B1, BSEP and MRP2, but not for OCT1, OCT2, OAT1, OATP1B3, P-gp and BCRP. Based on the *in vitro* studies, clinically meaningful interaction via inhibition of OCT1, OCT2, OAT1, OAT3, OATP1B3, BSEP and MRP2 by eluxadoline is unlikely. However, the *in vitro* studies were not adequate to establish the potential for eluxadoline to inhibit P-gp in the gut.

The applicant performed *in vitro* evaluation of eluxadoline interaction with transporters and found that it appears to be a *substrate for* OAT3, OATP1B1, BSEP, and MRP2, but not for OCT1, OCT2, OAT1, OATP1B3. It was not a good substrate for P-gp and BCRP. It was a *weak inhibitor of* OATP1B1, but did not significantly inhibit the other evaluated transporters (OAT1, OAT3, OCT1, OCT2, OATP1B3, P-gp, BCRP, BSEP, and MRP2) at a concentration of 400 ng/mL. IC_{50} values were not determined. For context, eluxadoline's systemic Cmax concentration at a 100 mg dose level ranges 2-4 ng/mL. However, eluxadoline concentrations in the gut may exceed the drug concentration tested in this study (I_{gut} = dose/250 mL=400 µg/mL) and impact transporters (such as BCRP and P-gp) present in the gut.

An *in vivo* study evaluated the impact of eluxadoline on rosuvastatin. Co-administration with eluxadoline resulted in a 40% increase in rosuvastatin AUC and an 18% increase in Cmax. Rosuvastatin is a substrate for both BCRP and OATP1B1, and it is not clear whether the impact on exposure occurs through one or the other transporter vs. both. However, the reviewers considered this *in vivo* study adequate to characterize the potential impact of gut levels of eluxadoline on BCRP, since the magnitude of the overall observed impact was not considered significant (indicating that even if 100% of the effects were due to BCRP, the impact was not substantive). However, the Clinical pharmacology reviewer stated, "We recommend caution should be exercised when rosuvastatin is coadministered with eluxadoline." Section 7 Drug Interactions of the product label will inform providers regarding the interaction and advise them to use the lowest effective rosuvistatin dose and monitor for rosuvastatin adverse events, as follows:

OATP1B1 and BCRP Substrate	
Clinical Impact:	VIBERZI may increase the exposure of co-administered OATP1B1 and BCRP substrates. Increased exposure to rosuvastatin when co-administered with VIBERZI with a potential for increased risk of myopathy/rhabdomyolysis *[see Clinical Pharmacology (12.3)]*.
Intervention:	Use the lowest effective dose (see prescribing information of rosuvastatin for additional information on recommended dosing).

The reviewers concluded that the applicant had submitted adequate information to support that the impact of eluxadoline on gut BCRP. However, given the absence of similar in vivo information of P-gp, the reviewers recommended a PMC to further evaluate the impact of eluxadoline on P-gp through *in vitro*, and possibly, follow-on *in vivo* studies. I concur. The approval letter will include the following PMC:

2901-7 Conduct an *in vitro* study to estimate the IC_{50} (or K_i) value of eluxadoline with respect to P-gp and predict the *in vivo* relevance of this interaction.

Final Protocol Submission: 01/01/2016
Study Completion: 12/31/2016
Final Report Submission: 03/31/2017

The applicant conducted an *in vivo* study of the impact of co-administration of cyclosporine (an inhibitor of OATP1B1, MRP2, P-gp, BCRP and OATP1B3) on eluxadoline exposure. In this study, eluxadoline AUC increased 4.4 fold and the Cmax increased 6.2 fold. The product label's Section 7 Drug Interactions (table of clinically relevant interactions affecting eluxadoline levels) will include a table that recommends reducing the eluxadoline dose to 75 mg in patients who must take cyclosporine concomitantly. (See below.) It will instruct providers to monitor patients for impaired mental or physical abilities need to perform potentially hazardous activities (driving, operating heavy machinery) and to monitor for adverse reactions related to eluxadoline. This information will appear under a header of "OATP1B1 Inhibitors" because the Clinical Pharmacology reviewers concluded that the observed increased exposure was most likely mediated via cyclosporine's impact on OATP1B1 transporters.

OATP1B1 Inhibitors	
Clinical Impact:	Increased exposure to eluxadoline when coadministered with cyclosporine *[see Clinical Pharmacology (12.3)]*
Intervention:	Administer VIBERZI at a dose of 75 mg twice daily *[see Dosage and Administration (2)]* and monitor patients for impaired mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery and for other eluxadoline-related adverse reactions *[see Adverse Reactions (6.1)]*.
Examples:	cyclosporine, gemfibrozil, antiretrovirals (atazanavir, lopinavir, ritonavir, saquinavir, tipranavir), rifampin, eltrombopag

Thorough QTc Study: The QT-IRT (Interdisciplinary Review Team) concluded that there was no significant QTc prolongation observed when eluxadoline 100 mg and 1000 mg (supratherapeutic dose) were administered to healthy subjects. The following table, which summarizes the data from the thorough QT study, is reproduced from the QT-IRT team review.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for JNJ-27018966 (100 mg and 1000 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
JNJ-27018966 100 mg	0.5	1.3	(-0.3, 2.8)
JNJ-27018966 1000 mg	2	3.6	(1.6, 5.6)
Moxifloxacin 400 mg*	1	11.9	(10.3, 13.4)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points are 9.7 ms.

The supratherapeutic dose (1000 mg) produced mean C_{max} values 10-fold greater than the mean C_{max} associated with the therapeutic dose (100 mg). This Cmax exceeds the Cmax expected with coadministration with cyclosporine (6.2 fold increase); however, it is lower than that expected with severe hepatic impairment (16 fold increase). The product will be contraindicated in patients with severe hepatic impairment.

6. Clinical Microbiology

Not applicable. The product is not an antimicrobrial product.

7. Clinical/Statistical-Efficacy

The applicant submitted the results of two large randomized, placebo controlled, phase 3 trials to establish the efficacy of eluxadoline for the proposed IBS-d indication. One trial (IBS-3002) was 26 weeks in duration (N=1146) and one (IBS-3001) was 52 weeks in duration (N=1282). Two dose levels of eluxadoline were compared to placebo in each of these trials: 75 mg BID and 100 mg BID. Efficacy analyses in both trials were responder analyses based on a composite endpoint that incorporated pain response and stool consistency response, based on Bristol Stool Scale Score (BSSS). Data were obtained from daily electronic diaries. The prespecified efficacy analyses were at Weeks 12 and 26 in Study IBS 3001. The blinded and controlled continuation to Week 52 was intended for obtaining controlled, long term safety data. The efficacy analysis in Study IBS -3002 occurred at week 26; however, this trial included a 4 week single blind "withdrawal" period. These trials were international trials, but the majority of sites and patients in both trials were in the US. (The other countries were Canada and the UK.)

The following table summarizes the FDA's Guidance to Industry regarding eligibility criteria and responder definitions for IBS-D trials.

Table 2: Summary of FDA Guidance to Industry for IBS-D Trial Eligibility Criteria and Responder Definitions

Primary Endpoint	Entry Criteria	Responder Definition
Abdominal Pain	Weekly average of worst abdominal pain in past 24 h score of ≥ 3.0 on a 0 to 10 points scale	Weekly responder = decrease in weekly average of worst abdominal pain in past 24 h score of at least 30% compared with baseline Daily Responder = decrease in worst abdominal pain in the past 24 h score of at least 30% compared with baseline
AND		
Stool Consistency	At least 2 days per week with at least one stool that has a consistency of Type 6 or Type 7 BSS	Weekly responder = decrease at least 50% in the number of days per week with at least one stool that has a consistency of Type 6 or 7 compared with baseline Daily responder = a patient whose stool consistency is less than 5 for all bowel movements on that day or no bowel movement

The key eligibility criteria for the two phase 3 trials submitted in this NDA were similar to those outlined in the Guidance. The average worst 24 hour pain score over the week prior to randomization was required to be *greater than* 3.0 on a scale of 0-10 (as compared to a score that could include 3, according to the Guidance). The stool consistency criterion was "Average stool consistency score by BSS of ≥ 5.5 and at least 5 days with a BSS ≥ 5 on a 1 to 7 scale over the week prior to randomization", which was not worded exactly the same as recommended in the Guidance. However, in order to have a BSS of at least 5.5 with at least 5 days being 5, the remaining two days of the week would have to exceed 5 (which is consistent with the Guidance). It should be noted that patients were required to have not been taking loperamide rescue mediation within 14 days prior to randomization.

From a safety standpoint, there are some key eligibility criteria that are important to consider related to the mu opioid agonist mechanism of the product. Patients with a history of pancreatitis of any etiology or biliary duct disease (excluding gall stones), or a history of Sphincter of Oddi dysfunction were excluded. Consistent with this, patients with serum lipase elevated >2 times the upper limit of normal in prescreening laboratory assessments were excluded. In addition patients with a history of cholecystectomy with any history of post cholecystectomy biliary tract pain were excluded, as were patients with a history of major gastric, hepatic, pancreatic or intestinal surgery (excluding appendectomy, hemorrhoidectomy, or polypectomy greater than 3 months postop were allowed).

Rescue loperamide was allowed post randomization, during the double blind treatment period, for uncontrolled diarrhea. Loperamide use was captured in the electronic diary.

The primary endpoint in both phase 3 trials was defined as follows (reproduced from Dr. Muldowney's Clinical Review):

- Proportion of composite responders over the initial 12 week double-blind period. A patient was a composite responder if he or she met the *daily response criteria for at least 50% of the days* (emphasis added) with diary

entries during Weeks 1 – 12. A patient was a *daily responder* [emphasis added] if he or she met **both** of the following criteria:

- Daily pain response: worst abdominal pain scores in the past 24 hours improved by ≥ 30% compared to baseline, where baseline was the average of daily worst abdominal pain score the week prior to randomization
- Daily stool consistency response: BSS score <5 or the absence of a bowel movement if accompanied by ≥30% improvement in worst abdominal pain compared to baseline pain.

To be eligible to be a responder, a patient must have had a minimum of 60 days of diary entries over the 12-week interval (70% diary entry completion). Any patient with fewer than the minimum days of diary entries was considered a non-responder.

The primary endpoint was assessed at 12 weeks for the purposes of regulatory review in the United States. The endpoint was assessed at 26 weeks for the purposes of regulatory review by EMA. For the 26 week analysis, there was a requirement to have at least 110 days of diary entries to be eligible for evaluation as a responder. The Statistical reviewer confirmed that there was no requirement that the missing data days must be distributed evenly over time (for example, there was no requirement that there could be no more than two missing days per week); however, she said that there was a similar pattern of missing data among the study arms.

Multiple secondary endpoints were prespecified by the applicant, including but not limited to, pain responder analyses and stool consistency analyses. These secondary analyses of the individual components of the composite endpoint included evaluation by multiple defined intervals: 12 week, 26 week, and each 4 week period. There was no prespecified plan for managing alpha spending beyond the primary efficacy analysis, and this became a major review issue that impacted labeling negotiations regarding which secondary analyses should be appropriately included in Section 14 Clinical Studies.

A number of sensitivity analyses were conducted by the applicant, and the Statistical reviewer also conducted her own mixed effect model for repeated measures analysis (MMRM analysis) of longitudinal pain data to explore impact of missing data. The Statistical reviewer reported that exploratory analyses with differing data handling conventions for missing data did not have an impact on overall efficacy findings.

The following table summarizes the primary efficacy analyses for the two phase 3 trials submitted in the NDA (composite responder analysis). The table will appear in product labeling. Both the US- and EMA- preferred primary analyses will be presented (12 week analysis and 26 week analysis). The results of both the 100 mg dose level and the 75 mg dose level will be presented because the label will include the 75 mg dose in the Dose and Administration section for patients who do not have a gallbladder, are unable to tolerate the 100 mg dose level, who are receiving concomitant OATP1B1 inhibitors, or who have mild or moderate hepatic impairment. The p value will only be included for the primary analysis prespecified for US regulatory review (12 week analysis for the composite responder definition). The results of the individual components, analyzed for the same time periods as the primary analyses (weeks 12 and 26) were also presented as this information was considered clinically relevant, given that they were the components of the composite primary endpoint. Although the confidence intervals are presented for these individual component analyses, the p values were not, as there was no prespecified plan for managing alpha for the secondary endpoint analyses.

Table 3: Summary of Efficacy from Study 3001(Study 1) and Study 3002 (Study 2)

	Study 1			Study 2		
	VIBERZI 100mg twice daily n=426	**VIBERZI 75mg twice daily n=427**	**PBO n=427**	**VIBERZI 100mg twice daily n=382**	**VIBERZI 75mg twice daily n=381**	**PBO n=382**
Composite[1] Response over 12 weeks						
Responder rates	25%	24%	17%	30%	29%	16%
Treatment difference	8%[2]	7%[4]		13%[3]	13%[3]	
95% CI (%)	(2.6, 13.5)	(1.4, 12.2)		(7.5, 19.2)	(6.8, 18.5)	
Composite Response over 26 weeks						
Responder rates	29%	23%	19%	33%	30%	20%
Treatment difference	10%	4%		13%	10%	
95% CI (%)	(4.7, 16.1)	(-1.0, 9.9)		(6.4, 18.8)	(4.2, 16.4)	
Abdominal Pain Response Improved ≥30% over 12 weeks						
Responder rates	43%	42%	40%	51%	48%	45%
Treatment difference	3%	2%		6%	3%	
95% CI (%)	(-3.0, 10.2)	(-3.8, 9.4)		(-1.3, 12.8)	(-4.3, 9.8)	
BSS <5 Response over 12 weeks						
Responder rates	34%	30%	22%	36%	37%	21%
Treatment difference	12%	8%		15%	16%	
95% CI (%)	(6.3, 18.2)	(2.1, 13.8)		(8.4, 21.0)	(9.7, 22.4)	

[1]Composite= Simultaneous improvement of Worst Abdominal Pain (WAP) by ≥30% and Bristol Stool Score (BSS) < 5 on the same day for ≥ 50% of days over the interval
[2] $P<0.01$
[3] $P<0.001$
[4] $P<0.05$

Of note, the analyses of the primary endpoint for both the 12 week and 26 week analyses were statistically significant for the 100 mg dose level in both trials. However, for the 75 mg dose level, there were some differences between the trials, depending on the time of analysis, i.e., 12 weeks vs. 26 weeks. The treatment difference relative to placebo was similar between the 75 mg and 100 mg dose levels in both trials in the 12 week analysis. However, at 26 weeks, the confidence intervals for the difference in composite response includes zero in the comparison of 75 mg to placebo in one of the trials. The treatment difference relative to placebo was numerically lower in the 75 mg arm than in the 100 mg arm in both trials at the 26 week analysis.

Efficacy, as measured by a responder definition of patients who experience both an improvement in stool consistency and pain, was established for the 100 mg dose level at both 12 weeks and 26 weeks (6 months). When the individual components of the

composite are evaluated separately at the same time points, the data show that eluxadoline's major treatment impact is in improving stool consistency (BSS). The treatment effect difference at the 100 mg dose level (relative to placebo) is very similar between the BSS responder analysis and the composite responder analysis in one trial (delta 15% vs. 13%, respectively). In one of the trials the treatment effect for the individual component BSS responder analysis was numerically higher than the composite (delta of 12% vs. 8 %, respectively).

In contrast, the treatment effect difference (relative to placebo) at the 100 mg dose level for the individual pain responder analysis is much lower than that observed for the composite analysis in both trials: 4% vs. 8% in one and 6% vs. 13% in the other. The proportion of pain responders was lower than the proportion of BSS responders in both eluxadoline arms and placebo; however, the pain response in the placebo arm observed in the individual pain endpoint analysis was nearly double that of the placebo response for the individual BSS analysis. When the applicant explored alternative definitions of pain response in a pooled analysis, use of a 50% reduction in pain score as a responder definition resulted in a decrease in proportion of pain responders (in the individual component analysis) in both treatment and placebo arms. In one study the treatment difference for the individual pain response analysis between eluxadoline and placebo increased from a delta of 3% (using the 30% pain score reduction definition) to 6%, indicating that the placebo responder rate decreased more than eluxadoline responder rate with the more conservative pain responder definition. However, in the other study, the delta between the eluxadoline pain responder rate and the placebo rate remained stable relative to that observed with the prespecified 30% reduction responder criterion.

The applicant proposed (b) (4) (b) (4) The reviewers did not concur (b) (4) (b) (4) Although the reviewers did not agree to (b) (4) they did agree that the label could include a general sentence describing the numerically higher composite response observed in the 4 week interval analyses.

8. Safety

As stated in the Clinical Review by Dr. Laurie Muldowney, "A total of 2562 subjects have been exposed to eluxadoline during the clinical development program, including 520 and 541 patients exposed to 6 months of 75 mg and 100 mg BID treatment, respectively. In addition, over 340 patients were exposed to 12 months of treatment with eluxadoline 75mg or 100mg BID." The label will state that patients should start treatment at the 100 mg BID dose level, with the exception of patients who don't have a gall bladder, patients with mild or moderate hepatic impairment and patients who are taking concomitant OATP1B1 inhibitors, for whom the 75 mg BID dose will be recommended. The number of patients in the safety dataset that had been exposed to at least 12 months of treatment with eluxadoline 100 mg BID was 170.

Given eluxadoline's mechanism of action, abdominal pain events and constipation events were of particular interest to the reviewers as they conducted the safety review of this NDA. Mu opioid agonism would be expected to decrease gastrointestinal motility resulting in constipation. Although the drug is intended to treat abdominal pain, sphincter of Oddi

spasm (SOS) is a class effect of mu opioid agonists. SOS is generally associated with abdominal or biliary-type pain with or without abnormal liver enzymes, and can present as pancreatitis. Furthermore, even though it is from a different drug class, given that the currently approved product for treatment of this condition (IBS-d), alosetron, is associated with severe complications of constipation and ischemic colitis, the safety database was carefully examined for evidence of the adverse reactions that appear in the alosetron label (as described earlier in this review in Section 2 Background of this review).

In the pooled phase 2 and 3 safety analysis, eluxadoline 75 mg and 100 mg BID dose levels had similar rates of serious adverse events and adverse events leading to discontinuation, which is shown in the table below (reproduced from Dr. Muldowney's Clinical review).

Table 4: Overview of Adverse Events – Pooled Phase 2 and 3 Studies, All Doses (Table 44 in the Clinical Review)

	Eluxadoline 75 mg BID N[a] = 803		Eluxadoline 100 mg BID N[a] = 976		Placebo BID N[a] = 972	
	n (%)	Events	n (%)	Events	n (%)	Events
Adverse events	484 (60.3)	1562	566 (58.0)	1808	534 (54.9)	1588
Serious AEs	35 (4.4)	41	41 (4.2)	66	25 (2.6)	35
Related serious AEs	5 (0.6)	5	6 (0.6)	8	0	0
Deaths[a]	0	0	0	0	0	0
AEs leading to discontinuation	67 (8.3)	68	80 (8.2)	84	42 (4.3)	46

Source: Medical officer created table from the Sponsor's ISS ADAE dataset
[a] The Safety Analysis Set for the MO reviews differs from the Sponsor's safety analysis set due to patients who were misallocated drug. These patients were counted twice in the Sponsor's safety analysis set but were only included in once (in their planned treatment arm) for the MO analysis. This accounts for 4 patients in eluxadoline 75mg, 56 patients in eluxadoline
100mg, and 3 patients in placebo.

The proportion of patients that had at least 1 SAE in the pooled phase 2 and 3 safety data was similar between the 75 mg BID and 100 mg BID eluxadoline dose levels (4.2% and 4.0%, respectively), and the proportions exceeded that observed with placebo (2.6%). There was one death identified by the Clinical Reviewer, and she did not consider it related to eluxadoline. The patient was found dead in the home (b) (6) days of the last dose of drug, after (b) (6) days of exposure. (Treatment was initiated at 75 mg BID, and then increased in the last 31 days of exposure to 100 mg BID). Given the patients multiple comorbidities, (including morbid obesity, diabetes, hypertension, hyperlipidemia, sleep apnea), multiple concomitant medications (including, but not limited to, valproate, sumatriptan, liraglutide, vilazodone, atorvastatin, furosemide, heparin, eclecoxib, zolpidem, amitriptyline, atenolol and alprazolam), and 3 week interval from last eluxadoline exposure, the Clinical reviewer agreed that the death was most likely related to the patient's comorbidities.

The most common adverse reactions were gastrointestinal, and the most commonly reported Serious Adverse Events (SAEs) were categorized gastrointestinal disorders. The proportion of patients with gastrointestinal SAEs was similar between the two eluxadoline dose levels (1.0% vs. 1.3%), and both were higher than the placebo arm (0.4%). There were 2 hepatobiliary disorder SAEs in the eluxadoline 100 mg arm patients vs. none in the 75 mg and placebo arms. The most common SAE was pancreatitis (11 cases) – all in the eluxadoline arms. There was a single SAE of ischemic colitis in the safety database, and it occurred in a patient treated with eluxadoline 100 mg. In addition there was a single report of an SAE of small bowel obstruction in each of the placebo arm and the eluxadoline 100 mg arm. The ischemic colitis case occurred 19 days after starting treatment with eluxadoline 100 mg BID, but the Clinical Reviewer did not consider the case to be treatment related. I concur with her evaluation. Furthermore, she explored the safety data

base for evidence of events that may have been unrecognized/unreported ischemic colitis events and found no evidence suggesting a signal of ischemic colitis associated with eluxadoline exposure. The number of adverse events of rectal hemorrhage or hematochezia was similar across arms in the combined populations from the phase 2 and 3 trials [75mg = 5 (0.6%); 100mg = 7 (0.7%); placebo = 9 (0.9%)].

Abdominal Pain. Using a broad search of MedDRA terms for abdominal pain (abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness), the Clinical reviewer noted that there was a similar proportion of patients who reported abdominal pain adverse events with eluxadoline 100 mg relative to the 75 mg dose. Both were somewhat higher than placebo. Based on this broad capture, the proportion of patients with an abdominal pain AE was 8.6% (69/807) in the eluxadoline 75 mg BID arm, 8.9% (92/1032) in the 100 mg BID arm patient s and 5.5% (54/975) in the placebo arm patients. If the search was narrowed to "abdominal pain" only, the proportions decreased but the pattern was similar: 4.1% for 75mg, 4.6% for 100mg, and 2.6% for placebo. The proportion of patients who discontinued from the phase 2 and 3 studies due to abdominal pain was also similar between the two dose levels (1.49% in the eluxadoline 75 mg BID group and 1.45% in the 100 mg BID group). Of those patients who discontinued due to abdominal pain, 3/12 and 3/15 in the 75mg and 100 mg (respectively) arms were categorized as serious events. None were considered serious in the placebo arm. Both exceeded the proportion of patients in the placebo arm, i.e., 0.3%. The proportion of the abdominal pain events categorized as severe was numerically higher in the 100 mg eluxadoline arm than in the 75 mg arm [75 mg: 4/69 (6%) events; 100 mg: 13/92(14%) events]. When the proportion of severe abdominal pain adverse events was compared between dose levels, using the total study population treated at that dose level as the denominator, the rate of severe abdominal pain adverse events was also numerically higher in the 100 mg arm than the 75 mg arm: 1.3% vs. 0.5%.

The Clinical Reviewer expressed concern about the higher proportion of patients with adverse reactions reported as abdominal pain relative to placebo, given that the product is intended to treat IBS, and abdominal pain is a key symptom that defines the condition. The applicant asserted that most of the abdominal pain AEs could be attributable to sphincter of Oddi spasm; however, the Clinical Reviewer noted that give the lack of laboratory data to help adjudicate the etiology, the applicant's assertion could not be definitively proven. The applicant's program did incorporate a Hepatobiliary and Pancreatitis Adjudication Committee that evaluated abdominal pain cases for evidence of hepatobiliary/pancreatic origin, which I will describe further below.

When the abdominal pain AEs were tabulated based on terms limited to "abdominal pain", 18/47 (38%) abdominal pain AEs in the eluxadoline 100 mg BID arm occurred in patients with a history of cholecystectomy, and 8/33 (24%) of the events in the 75 mg arm occurred in patients with this history (compared to 6/25 [24%] events in the placebo arm). The majority of the abdominal pain AEs in the eluxadoline 100 mg arm occurred in the first week of treatment (28/47, 60%), whereas 11/33 (33%) and 5/25 (20%) occurred in the first week of treatment in the eluxadoline 75 mg and placebo arms, respectively. When the rates were calculated based on a denominator equal to the number of patients treated at the dose level who had a history of prior cholecystectomy, the proportion of those patients in the eluxadoline 100 mg arms who developed abdominal pain was double that of patients with a similar history in the eluxadoline 75 mg arms, 9.8% vs. 4.8%. The rate in the lower dose 75 mg eluxadoline arm was similar to that of placebo (3.8%). When the MEDRA terms used for this analysis were expanded, the rates of abdominal pain in the prior cholecystectomy subgroup across all arms increased, however, the distribution was similar: 15.8% eluxadoline 100 mg, 9.7% eluxadoline 75 mg, 9.5% placebo. When the rates of abdominal pain AEs *within* treatment arms were compared between patients with a history of cholecystectomy vs patients who did not have a history of cholecystectomy, there was a similar proportion of abdominal pain AEs between the cholecystectomy subgroups within the 75 mg treatment arm (4.8% in positive history vs. 3.9% negative history) and within the placebo treatment arm (3.8% in the positive history subgroup vs. 2.5% in the negative

history subgroup). In contrast, within the 100 mg eluxadoline arm, there was a much higher rate of abdominal pain AEs in the prior cholecystectomy subgroup than in the patients without a history of cholecystectomy (9.8% vs. 3.7%).

Table 5: Summary of Abdominal Pain Adverse Events from Pooled Phase 2 and 3 (reproduced from Table 49 in the Clinical Review), search limited to events coded "abdominal pain".

	Incidence of Abdominal Pain Adverse Events		
	Eluxadoline 75mg BID (N=807)	Eluxadoline 100mg BID (N=1032)	Placebo BID (N=975)
Any AE of Abdominal Pain[a], n (%)			
Overall	33 (4.1)	47 (4.6)	25 (2.6)
Within first week	11 (1.4)	28 (2.7)	5 (0.5)
Within first 2 weeks	14 (1.7)	29 (2.8)	7 (0.7)
Within first 12 weeks	26 (3.2)	39 (3.8)	18 (1.8)
Initial AE of Abdominal Pain after First Week, n(%)	22 (2.7)	19 (1.8)	20 (2.1)
Any AE of Abdominal Pain Leading to Discontinuation, n(%)[b]			
Overall	9 (1.1)	11 (1.1)	3 (0.3)
Within the first week	4 (0.5)	7 (0.7)	1 (0.1)
Any AE of Abdominal Pain by Prior Cholecystectomy Status[c], n/N(%)			
Overall (prior cholecystectomy)	8/165 (4.8)	18/183 (9.8)	6/494 (3.8)
Overall (no prior cholecystectomy)	25/642 (3.9)	25/676 (3.7)	16/650 (2.5)

Source: Response to Agency Questions During 10Dec2014 Midcycle Communication Meeting, Received 12January2015

[a] This summary includes only AEs coded with the preferred term "abdominal pain"

[b] Incidence calculated as the difference of "Overall" – "Within first week" rows presented in Table 1. Percentage of patients is based on overall treatment group N.

[b] Prior cholecystectomy status was prospectively captured in Phase 3 studies only. AE summary by prior cholecystectomy status includes only Phase 3 patients, with N for patients with/without prior cholecystectomy

Given the observed pattern of the higher proportion that occurred in patients with a history of cholecystectomy, and given the early onset of pain after initiation of eluxadoline treatment, the Clinical Reviewer concluded that a common etiology underlying the abdominal pain was treatment related sphincter of Oddi spasm.

The sphincter of Oddi surrounds the duct formed by joining of the common bile duct and the main pancreatic duct, and controls movement of bile and pancreatic juices into the duodenum. Sphincter of Oddi spasm pain is described in the literature as colicky abdominal pain, but it can mimic renal colic, intestinal perforation, and myocardial ischemia.[3] When induced by narcotics, it reportedly has onset at 5-20 minutes post administration of the narcotic. Pancreatitis has been reported associated with sphincter of Oddi dysfunction. Hastier, et al[4] reported a case series of patients with pancreatitis related to codeine ingestion in which all of the patients were status post cholecystectomy. The authors noted that increased sphincter of Oddi pressure has been shown in patients after cholecystectomy, due to fibrosis or smooth muscle hyperplasia. They postulated that the codeine ingestion caused "a rise in biliary and/or pancreatic sphincter pressure by exacerbating preexisting sphincter of Oddi disease or as a consequence of reduced storage capacity of the biliary tract." Presence of the gall bladder, which acts as a bile reservoir, would allow for

[3] Butler K, Selden B and Pollack C. Journal of Emergency Medicine, Vol 21, No.2; pp129-131, 2001.

[4] Hastier, P, et al. A New Source of Drug-Induced Acute Pancreatitis: Codeine. Am J Gastroenterology; Vol. 95, No. 11, 2000.

decompression of the biliary tract. Absence of the gall bladder does not allow for this compensatory response to decreased movement of bile past the sphincter.

The external Hepatobiliary and Pancreatitis Adjudication Committee evaluated abdominal pain AEs that were suspected cases of Sphincter of Oddi spasm (which was defined as an acute reversible pancreatic or biliary tract obstruction) to determine if they met case definitions for pancreatitis (2/3 of the following criteria: abdominal pain suggestive of pancreatitis based on epigastric localization with radiation in to the back, elevated amylase or lipase ≥3 times ULN, and/or CT/MRI/ultrasound findings characteristic of pancreatitis) and acute hepatobiliary events (all of: epigastric or right upper quadrant pain, ALT or AST ≥3 times ULN or 2x elevated baseline and event prompted study drug withdrawal). It also adjudicated whether the pain was related to sphincter of Oddi spasm.

Of 37 "suspected" events submitted to the committee for adjudication:

- 9 were adjudicated as having **pancreatitis** and
  - 3 of these were adjudicated as having symptoms consistent with sphincter of Oddi spasm.
- 9 additional cases were adjudicated as having **acute biliary events**.
- All 18 cases (9 pancreatitis + 9 acute biliary events) had been treated with eluxadoline.

Among the 9 cases adjudicated as meeting the definition of **pancreatitis**:

- the 3 also considered to have symptoms consistent with sphincter of Oddi spasm presented with signs (elevated enzymes) and symptoms within 1 dose (in two patients) or 2 doses (one patient) of eluxadoline.
- Among the 6 patients without sphincter of Oddi spasm symptoms,
  - 4 had significant alcohol consumption as the suspected underlying etiology. Events occurred in a range of 18 days to 10 weeks after starting treatment with eluxadoline.
  - In one of the remaining two patients, the last dose of eluxadoline was 15 days prior to developing pancreatitis symptoms and the pancreatitis was attributed to concomitant antibiotic, clarithromycin.
  - In the other one of the remaining two patients, presentation occurred after 26 weeks of treatment, and biliary sludge/thickened bile was observed on MRI.

Among the 9 patients who were adjudicated as having **acute hepatobiliary events**, all were also adjudicated as also have symptoms consistent with sphincter of Oddi spasm. Seven of the 9 experienced symptom onset within the first week of treatment and one required hospitalization (for management of nausea and vomiting). All resolved with discontinuation of eluxadoline.

The following table, which is reproduced from the Clinical review, summarizes these events by number of patients exposed.

Table 6: Rates of Adjudicated Hepatobiliary and Pancreatic Events in Eluxadoline Exposed Subjects (reproduced Table 53 in Clinical Review)

Event	Events/exposure[1]	Event rate
Rate of adjudicated hepatobiliary spasm overall	9/2562	0.35%
Rate of adjudicated pancreatitis overall	9/2562	0.35%
Rate of pancreatitis excluding single subject off treatment >2 weeks	8/2562	0.31%
Rate of pancreatitis OR lipase elevation adjudicated as SO spasm	4/2562	0.16%
Rate of pancreatitis NOT adjudicated as SO spasm	6/2562	0.23%
Rate of adjudicated SO spasm (pancreatic and hepatobiliary) overall[2]	13/2562	0.51%
Rate of adjudicated SO spasm (pancreatic and hepatobiliary) in Phase 2 and Phase 3	13/2232	0.58%
Rate of adjudicated SO spasm (pancreatic and hepatobiliary) in Phase 3	10/1615	0.62%
Rate of adjudicated SO spasm (pancreatic and hepatobiliary) in patients s/p cholecystectomy in Phase 3[3]	10/238	4.2%

Source: Modified from Applicant's HPAC Summary Table 4-6

[1] 2562 represents total unique human exposure in eluxadoline Phase 1, Phase 2, and Phase 3 studies. 1615 represents unique human exposures in the eluxadoline Phase 3 studies.

[2] Adjudicated SO spasm includes 3 cases of pancreatitis, 9 cases of hepatobiliary events, and 1 case of SO spasm not meeting the criteria for pancreatitis

[3] Cholecystectomy status was collected uniformly only during Phase 3 Studies, thus only Phase 3 events were included.

The Clinical reviewer examined mu opioid agonist product labels, including codeine and tapentadol, and noted that sphincter of Oddi spasm is described in their Warnings and Precautions sections. After literature review, she concluded the rate of Sphincter of Oddi spasm observed with eluxadoline is consistent with that reported for approved opiates.

Constipation. The proportion of patients with constipation in the eluxadoline arms of the phase 2/3 trials was higher than placebo (75mg =7.4%; 100 mg =8.1%; placebo =2.5%). The proportion discontinuing due to constipation was similar between 100 mg and 75 mg, 1.5% vs. 1.1%, respectively. Both were numerically higher than placebo, 0.3%. None of the constipation events were SAEs. Most were graded mild in severity.

The study included a prospective definition of constipation based on stool frequency (absence of bowel movement on 4 consecutive days) and a retrospective definition based on Bristol Stool Score (average BSS score < 2 over any study week). These data were entered in a daily diary via the IVRS system, and exploratory analyses of "confirmed constipation" were based on these definitions. These data were presented in the Clinical review by Quarter (time on study). The following two tables summarize constipation by quarter reported as "confirmed constipation" based on number of bowel movements or BSS (Table 8 below) and, for the purposes of comparison, constipation reported as an adverse event (Table 7).

Table 7: Summary of Constipation AEs by Quarter[a] – Pooled Phase 2/3 Studies (Table 54 in Clinical Review)

	Number (%) of Patients		
	Eluxadoline 75mg BID (N=807)	Eluxadoline 100mg BID (N=1032)	Placebo BID (N=975)
Number of patients with ≥ 1 constipation AE overall	60 (7.4)	84 (8.1)	24 (2.5)
Quarter 1	53 (6.6)	64 (6.2)	20 (2.1)
Quarter 2	9 (1.4)	15 (1.9)	2 (0.3)
Quarter 3	1 (0.2)	4 (0.6)	3 (0.5)
Quarter 4	2 (0.7)	5 (1.6)	1 (0.4)

Source: Modified from Applicant ISS Amendment Table 2.68

[a] A quarter was defined as a 13-week period, starting from date of first study drug. Quarters 3 and 4 include only data from the 52-week study, IBS-3001.

Table 8: Pooled Analysis of Phase 2 and 3 Studies: IVRS-"Confirmed Constipation" by Quarter (Table 56 in Clinical Review)

	Number (%)[a] of Patients		
	Eluxadoline 75mg BID (N=807) n(%)N'	Eluxadoline 100mg BID (N=1032) n(%)N'	Placebo BID (N=975) n(%)N'
IVRS-confirmed constipation based on number of bowel movements[b]			
Quarter 1	23 (2.9) 27	37(3.8) 53	25 (2.6) 33
Quarter 2	18(2.8) 21	27 (3.6) 35	11 (1.4) 15
Quarter 3[e]	4 (0.7) 4	1 (0.2) 1	2 (0.3) 2
IVRS-confirmed constipation based on BSS score[d]			
Quarter 1	83 (10.3) 268	101 (10.3) 256	38 (3.9) 74
Quarter 2	70 (10.9) 270	57 (7.6) 222	31 (4.1) 66
Quarter 3[e]	26 (4.6) 54	21 (3.6) 41	9 (1.6) 18

Constipation by Quarter[b]

Source: Applicant's ISS Amendment Tables 2.69 and 2.70

[a] Percentages are based on available diary data at each time point.

[b] A quarter is defined as a 13 week period, starting from date of first dose of study drug. IVRS was only completed through the end of Week 26 for both studies, so no data is available for IVRS confirmed constipation for Quarter 4.

[c] IVRS-confirmed constipation based on number of bowel movements is defined as the absence of a bowel movement on at least 4 consecutive days, based on non-missing IVRS diary entries.

[d] IVRS-confirmed constipation based on BSS score is defined as a weekly average BSS score of <2 over any study quarter based on the IVRS diary entries

[e] Quarter 3 IVRS entries comprises only patients in the single-blind withdrawal phase of Study IBS-3002 and patients in Study IBS-3001 who attended their Week 26 visit after Day 182.

n is the number of subjects with one or more events in the quarter, N' is the number of events.

Exploration of these data, comparing the adverse events of constipated reported vs. what patients reported on a day to day basis regarding stool frequency and stool form, reveals the following:

- The proportion of constipation adverse events (Table 7 above) dropped after the first quarter. In contrast, the "IVRS-Confirmed Constipation" rates did not drop with subsequent quarters, with either definition, i.e., the absence of bowel movement or stool consistency.
- The BSS score defined event quarterly rates of "IVRS-Confirmed Constipation" were higher than with the definition based on the absence of bowel movement over 4 days.
- The rate of "IVRS-Confirmed Constipation" based on absence of bowel movements was lower than the constipation adverse event rate in the first quarter. Note that the eluxadoline and placebo rates of IVRS-Confirmed Constipation based on absence of bowel movement rates in the first quarter were similar to each other.
- The rate of "IVRS-Confirmed Constipation" based on BSS was higher than the constipation adverse event rate in all quarters. The eluxadoline BSS-defined constipation rates were higher than placebo across the quarters.
- These data suggest that shifts in stool form to hard stools contributed to the constipation adverse events, and that these changes in stool consistency can persist over the course of treatment. Despite the persistence, patients were less likely to report constipation as an adverse event with the passage of time. Discontinuation of patients with constipation adverse events could have contributed to this reduction of adverse event reporting over time, however, the rate of discontinuation

was only 1.1% and 1.5% in the eluxadoline 75 mg and 100 mg arms, respectively.

Cardiovascular Safety. Eluxadoline is a mu-opioid receptor (μOR) agonist and a delta opioid receptor (δOR) antagonist. There is some evidence it is also a kappa opioid receptor (κOR) agonist. The Ki value for eluxadoline binding affinity for human mu receptors is 1.8 nM. The Nonclinical reviewer noted in his review the varying results of a series of *in vitro* human delta opioid receptor binding studies. The average Ki value from the series was 674 nM (ranging 367 to 1398 nM). In a direct comparison study of two different eluxadoline batches to reference compounds, the Ki values for human delta opioid receptors were 494 and 367 nM, respectively (average of the two values = 430 nM). The Ki value for human kappa opioid receptors has not been determined.

On June 11-12, 2014, an FDA Advisory Committee (AC) meeting (Anesthetic and Analgesic Drug Products Committee) was convened to discuss the necessity, timing, design and size of cardiovascular outcomes trials (CVOT) to support approval of products in the class of opioid receptor antagonists for the indication opioid-induced constipation in patients taking opioids for chronic pain. Alvimopan had previously been approved in May 2008 with a Risk Evaluation and Mitigation Strategy (REMS) because of an observation of an imbalance in myocardial infarctions that did not favor alvimopan in a single, long-term, controlled study in patients with OIC (chronic pain setting). Alvimopan is restricted to use in hospitalized patients only, and limited to a total of 15 doses.

At the time of the AC meeting, the Division was reviewing two mu opioid antagonist NDAs (methylnaltrexone and naloxegol) for the indication opioid-induced constipation in patients taking chronic opioids for noncancer pain. The Committee's input was sought regarding the strength of the signal of cardiovascular events in the alvimopan program and whether the signal was generalizable across the drug class. The Committee was unwilling to completely dismiss the myocardial infarction imbalance previously observed in the alvimopan study, and the Committee did not present a definitive argument for or against whether the observation should be considered a class concern. Although they could not exclude that the signal (which some members considered highly questionable or weak) was generalizable across the class, there was general support for requiring an adequate premarketing evaluation to exclude a cardiovascular safety signal. The Committee members varied on their perspective of what constituted an adequate evaluation to exclude a cardiovascular safety concern; however, there was, at a minimum, general support for requiring that premarketing clinical development plans for drugs in the class include a randomized, controlled trial of at least a year's duration with a minimum sample size in the range of the alvimopan trial in which the myocardial infarction imbalance was observed. The majority of the Committee did not support requiring a dedicated cardiovascular outcomes clinical trial to address this. Instead, they expressed support for a post marketing observational study conducted using electronic healthcare data.

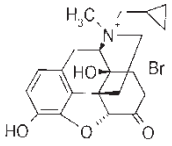
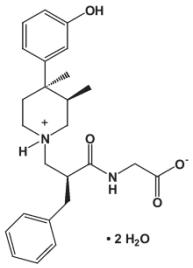
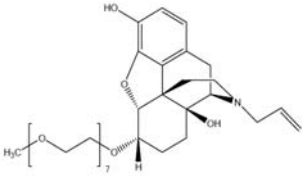
Ultimately the Division concluded that the premarketing safety assessment in the class should be a 12 month trial, ideally controlled, with a sample size similar to the alvimopam and naloxegol safety databases (not a CVOT). Although the premarketing trial goal would be to evaluate general safety of the drug over extended use, a prespecified plan to adequately capture/assess/adjudicate MACE events would need to be included to help assure adequate interpretation and assessment for any evidence of a CV signal. Such a sample size would be expected to have limited capability to detect a signal, unless the incremental increase in risk was quite large.

In the context of the issue of potential increased CV risk in the class, the Division concluded that a controlled, observational study could be a means of identifying a signal/safety risk with some degree of sensitivity (better than that associated with the "standard safety study" described in #3 above). A CVOT is the best way to identify and describe an incremental increase in cardiovascular risk; however, this was not supported by

the AC. Therefore, the methylnaltrexone and naloxegol approval letters included a PMR post-marketing safety study: an observational epidemiologic study comparing the drug to other treatments of opioid induced constipation in patients with chronic non-cancer pain. The primary outcome is a composite of major adverse cardiovascular events (MACE): CV death, nonfatal myocardial infarction and nonfatal stroke.

Although eluxadoline is a mu opioid *agonist*, it interacts with other opioid receptors, and like the mu opioid antagonists discussed above, it is a delta opioid receptor antagonist. If there is in fact a true CV signal associated with those drugs, the mechanism is not clear. It is possible that the mechanism could occur through interactions with opioid receptors other than the mu receptor. Delta opioid receptors are found in the heart and publications have explored their potential cardioprotective role during ischemia. The following table summarizes the binding affinities for human delta opioid receptors. As noted above, in multiple human delta opioid receptor assays, the eluxadoline Ki has ranged 430-674 nM, which is higher than alvimopam in the table below (5 nM) and naloxegol (32 nM) and similar to the Ki reported for methylnaltrexone (500 nM). Although the binding affinities for delta opioid receptors are similar between eluxadoline and methylnaltrexone, the Cmax exposure at the clinical dose level for methylnaltrexone (a subcutaneously administered product) is higher than that of eluxadoline (administered orally): 140 ng/mL vs. 2-4 ng/mL, respectively.

Table 9. Opioid Receptor Profiles and Clinical Use Information for Opioid Receptor Antagonists

	Methylnaltrexone (Relistor)	Alvimopan (Entereg)	Naloxegol (Movantik)
Chemical Structure:			
Indication:	Opioid-induced constipation	To accelerate time to upper and lower GI recovery following partial large or small bowel resection surgery with primary anastomosis	Opioid-induced constipation
Dose:	0.15-0.30 mg/kg	12 mg BID (0.48 mg/kg) for 7 days	12.5 or 25 mg once daily
Route of Administration:	Subcutaneous	Oral	Oral
μ opioid receptor	6 nM[1]	0.25 nM[1]	5 nM[2]
δ opioid receptor	500 nM[1]	5 nM[1]	32 nM[2]
κ opioid receptor	no comparative data[1]	no comparative data[1]	no comparative data[2]
- μ opioid receptor:	antagonist	antagonist	antagonist
- δ opioid receptor:	antagonist	antagonist	antagonist
- κ opioid receptor:	antagonist	antagonist	antagonist or weak partial agonist

1: Tsuruda et al., Naunyn-Schmiedeberg's Arch Pharmacol, 386:479-491, 2013.
2: Data generated from same laboratories as in Tsuruda et al., 2013.

The reviewers of the current NDA considered whether the clinical trial safety dataset presented for eluxadoline was adequate to assess for a cardiovascular signal, i.e., designed and with an enrollment consistent with the general AC recommendation described above (controlled trial of at least 12 months duration, sized similarly to the almivopam trial) and whether there was cause to require a PMR observational safety study as a condition of

approval of eluxadoline, to be consistent with the PMR for methylnaltrexone and naloxegol, in light of events observed in the safety dataset and the presence of shared delta opioid receptor antagonism with the mu opioid antagonists. They concluded that the clinical dataset in this NDA was generally adequate, as described in the AC discussion, because one of the phase 3 trials was a 52 week double blind placebo controlled trial that enrolled 1282 patients: 75mg = 429; 100 mg = 426 and placebo = 427. The alvimopan controlled trial in which the myocardial infarction imbalance was observed enrolled 538 patients in the alvimopan arm and 267 in the placebo arm.

As summarized in the CDTL review, the adverse event rates in the overall safety database for the pooled phase 2/3 trials for the umbrella "cardiac disorders" were 1.5%, 1.8% and 1.1% for the 75 mg, 100 mg, and placebo groups, respectively. The trials in the NDA did not include a committee to adjudicate cardiovascular events to determine whether they represented MACE events. The applicant evaluated the unadjudicated CV adverse events based on their own definition of MACE, which included non-fatal MI, non-fatal stroke, cardiovascular death, or requirement for a major cardiac procedure (CABG or coronary stent placement). This definition differs from the definition used by FDA, in that it included an additional element of major cardiac procedure.

The CDTL review reports the event tabulation based on the applicant's definition. They reported 8 total events (75 mg =2; 100 mg =3; placebo =3), but only 4 met a MACE definition that excluded the cardiac procedures and a transient ischemic attack (TIA, neurological event). These events all occurred in the two phase 3 trials (Study 3001 = 5 and Study 3002 = 2) and the phase 1 hepatic impairment single dose study IBS-1005 (one).

The 4 events defined by the FDA preferred definition (limited to non-fatal MI, non-fatal stroke, cardiovascular death) were evenly split between the two eluxadoline dose levels; none occurred in the placebo arm. The two events in the 75 mg arm occurred in the 12 month trial Study 3001, and of the two events in subjects exposed to 100 mg, one occurred in Study 3001 and one in the hepatic impairment single dose study IBS-1005.

The CDTL review points out that 2 of the events in eluxadoline exposed patients occurred remotely to drug exposure. One, in the 75 mg arm, was a sudden death (patient found in the home) (b) (6) weeks after stopping study drug. The hepatic impairment study patient had a myocardial infarction (b) (6) days after a single exposure to 100 mg study drug. This patient had baseline moderate hepatic impairment (which is associated with 4-6 fold increase in exposure). I agree that the remoteness of the study drug exposure in these patients raises reasonable question about relatedness, particularly if the mechanism of CV toxicity is via delta opioid receptors, for which the literature indicates are cardioprotective (agonism) in the setting of ischemia. Given the mean elimination half-life of eluxadoline ranges from 3.7 - 6 hours, meaningful residual delta opioid antagonism from study drug seems unlikely in the patient with normal liver function (b) (6) weeks post exposure. The half-life in the moderate hepatic impairment subgroup of the hepatic impairment PK study was 21.78 hours. Therefore, the event (b) (6) days out from last dose in the patient with moderate hepatic impairment is also unlikely to be related based on temporal relationship.

Based on these considerations, the reviewers concluded that there was no suggestion of a cardiovascular signal in the overall safety data base, or within the 12 month phase 3 trial, Study 3001, which had a control arm and enrolled a similar number of subjects as the alvimopam trial. Within that trial, there were 3 apparent MACE events in eluxadoline treated patients vs. none in the placebo arm. One of the 3 events was not considered plausibly related due to onset remote from study drug exposure. In light of this relatively small imbalance, and the relatively low exposure to drug relative to methylnaltrexone, and the differences between the delta opioid receptor binding affinity for eluxadoline vs. alvimopam (and naloxegol), the review team concluded that there was no basis at this time for requiring a postmarketing CVOT or a postmarketing observational safety study for eluxadoline similar to those required for the mu opioid receptor antagonists. I concur.

Demographic/Drug interactions. There were nearly twice as many females than males in the combined phase 2 and 3 safety dataset. There was a higher rate of adverse events in females than males, and the rate of GI disorders AEs was somewhat higher in females (27.3% vs. 20.8%); however, the proportion experiencing SAEs was similar between sexes.

The Clinical reviewer conducted exploratory analyses of the pooled safety dataset based on age, which revealed a higher proportion of patients ≥65 years reported AEs than younger patients (66.7% vs. 55.6%) and the rate of SAEs was also higher in the older subgroup (7% vs. 3%). The proportion of GI AEs was 34% vs 24%. The rate of overall AEs that led to study discontinuation was also higher in the older subgroup: 11.9% vs. 6.4%. The subgroup ≥65 years was relatively small compared to those younger: 246 vs. 1989. The types of AEs reported were similar between the age subgroups – constipation, abdominal pain and nausea. The applicant was asked to confirm the results of these analyses. Their results were slightly different, but showed a similar pattern. The applicant's analyses will be presented in the label Section 8.5 Geriatric Use: "…a higher proportion of elderly patients than younger patients experienced adverse reactions (66% vs 59%), serious adverse reactions (9% vs 4%), and gastrointestinal adverse reactions (39% vs 28%)."

Laboratory evaluations. The clinical reviewer noted that there were patients in the trials who developed ALT's >3 X ULN, but the distribution was similar across arms. Similarly, the incidence of total bilirubin elevations >1.5 x ULN were comparable across arms (75mg = 1.9%; 100mg= 1.3%; placebo=1.2%). There were no cases that met Hy's Law. The following table from the Clinical review summarizes the rates of varying incremental increases of ALT above normal observed in the pooled phase 2 and 3 trials. The only band in which the eluxadoline arms appear higher than placebo was the >5 x ULN-10X ULN, in which the rate for each of the eluxadoline arms was 0.5% vs. 0.1% placebo. The Clinical reviewer notes in her review that proportion of patients with ALT values >3 x ULN appeared higher in the subset with a history of prior cholecystectomy. Some patients with higher incremental increases of ALT were adjudicated to have had Sphincter of Oddi spasm. One patient in the phase 2 trial who developed an ALT of 615 was diagnosed with acute hepatitis B infection.

Table 10: Post-Randomization Increase in ALT from Pooled Phase 2 and 3 Safety Analysis Set (Clinical Review Table 62)

	Number (%) of Patients		
Highest Post-Randomization Value	Eluxadoline 75mg BID (N=807)	Eluxadoline 100mg BID (N=1032)	Placebo BID (N=975)
Normal ALT at Baseline			
>1x ULN – 3xULN	114 (14.1)	126 (12.2)	128 (13.1)
>3xULN – 5xULN	5 (0.6)	4 (0.4)	4 (0.4)
>5xULN – 10xULN	4 (0.5)	5 (0.5)	1 (0.1)
>10xULN – 20xULN	1 (0.1)	1 (0.1)	0
>20xULN	1 (0.1)	0	0
Abnormal ALT at Baseline[a]			
>1x ULN – 3xULN	82 (10.2)	120 (11.6)	108 (11.1)
>3xULN – 5xULN	9 (1.1)	8 (0.8)	11 (1.1)
>5xULN – 10xULN	6 (0.7)	2 (0.2)	4 (0.4)
>10xULN – 20xULN	0	2 (0.2)	0
>20xULN	0	0	0

Source: Applicant Integrated Summary of Safety, Table 10-1

[a] Patients were eligible for study entry with ALT up to 3xULN.

Abuse Potential and Withdrawal. Refer to the Clinical review and the FDA Controlled Substance Staff (CSS) reviews for detailed analyses of adverse events that could inform abuse potential of eluxadoline. Adverse events of interest, including dizziness, fatigue, anxiety, depression and somnolence, were evaluated in the combined phase 2/3 safety datasets, and the rates were similar in distribution across the two dose levels and placebo. An exception was somnolence, in which the rate was numerically highest in the 100 mg group compared to both the 75 mg group and placebo (75mg = 0.1%; 100 mg=1.1%;

placebo = 0.3%). In addition, 0.2% (N=2) of patients treated with 100 mg in the combined clinical trials reported euphoria. The CSS reviewers noted that in the human abuse potential studies, which were conducted in subjects who were experienced recreational users of opioids, intranasal eluxadoline and supratherapeutic oral doses were reported in 14-28% of subjects. However, euphoria reports were less common with eluxadoline than oxycodone in these studies.

The subjective opiate withdrawal scale (SOWS) was employed in the phase 3 trials, to evaluate for withdrawal symptoms 0 to >3 days post stopping study drug. In addition, adverse events data were evaluated for evidence of withdrawal symptoms. There was a 2 week post treatment follow up period in one study (Study IBS-3001) and a 2 week single blind withdrawal period in Study IBS-3002 (however, SOWS was not completed in the latter). CSS reviewed the applicant's evaluation of human physical dependence and concluded that "The human physical dependence study was inadequately designed to evaluate whether chronic administration of eluxadoline produces withdrawal responses indicative of physical dependence." This was only assessed at a single time point in Study Study 3001 and the assessment tool was limited to SOWS. The applicant proposed language in the label (b) (4) the CSS and Clinical reviewers agreed that this was not appropriate for inclusion in the product label.

Hepatic Impairment. The Clinical Reviewer presented an exploration of adverse events rates in the pooled phase 2 and 3 studies in the subset of patients who had ALT >3 x ULN at study entry and in the subset who had an elevated bilirubin at baseline (above ULN but >3 mg/dl, as the latter was an exclusion criteria in the trials). The applicant's hepatic impairment study demonstrated increased eluxadoline exposure in patients with hepatic impairment (see Section 5 Clinical Pharmacology of this review). No definitive increase in rates of adverse events in the categories of GI disorders, infections/infestations, and nervous system disorders was noted in these two subgroups relative to the overall safety dataset, with the exception of an increase in nervous system disorders in the 100 mg arm patients with elevated baseline bilirubin (18.8% in the subgroup vs. 10.9% in the overall database). However, the significance of this is unclear as this subgroup was very small (n=32), and the rate of nervous system disorders in the elevated baseline bilirubin subgroup who received placebo was also elevated compared to the overall safety dataset (14.3%).

In the dedicated hepatic impairment study (single dose) dizziness was the most frequently reported AE (reported in 2, 1 and 1 subject in the mild, moderate and severe groups, respectively). One subject with mild hepatic impairment had an MI 13 days after study drug (as described above). One patient with severe impairment experienced an SAE of ileus 4 days after study drug administration.

Drug Drug interaction (loperamide). Review of the safety of concomitant administration of eluxadoline with loperamide is important, as it is likely "in the real world" that patients will take both medications concomitantly if distressed by diarrhea symptoms while initiating/taking eluxadoline. In the clinical trials, loperamide use was only permitted for acute management of diarrhea. In the combined phase 2/3 safety dataset, 272/807 patients in the 75 mg arms took at least one dose of rescue medication and 262/1032 in the 100 mg arms took rescue medication (compared to 295/975 of placebo arm patients). Comparisons of the rates of GI adverse events between the subgroup that took rescue medication vs. the overall pooled safety data set did not reveal a significant safety issue associated with rescue loperamide used concomitantly with eluxadoline. There was a numerically slightly higher rate of nausea adverse events in the eluxadoline arm subgroups that took rescue loperamide, which was not observed in the placebo arm. Constipation rates were similar between the two groups. , There was a small numeric increase in rate of abdominal pain AEs in the eluxadoline treated patients that received loperamide, which was also observed in the

placebo group patients that received rescue loperamide. This is summarized in the table below, reproduced from the Clinical Review.

Table 11 GI Adverse Events in Full Safety Set (combined phase 2/3) and in the Subgroup of Subjects that Received Loperamide as Rescue Medication (Table 66 in the Clinical Review).

GI Adverse Events In Full Safety Set			
System Organ Class Preferred Term	**Eluxadoline 75mg BID (N=807) n (%)**	**Eluxadoline 100mg BID (N=1032) n (%)**	**Placebo BID (N=975) n (%)**
Number of subjects with at least 1 GI Adverse Event	242 (30.0)	273 (26.5)	185 (19.0)
Nausea	65 (8.1)	73 (7.1)	49 (5.0)
Constipation	60 (7.4)	84 (8.1)	24 (2.5)
Abdominal pain	33 (4.1)	47 (4.6)	25 (2.6)
GI adverse events leading to discontinuation	38 (4.7)	51 (4.9)	17 (1.7)
Serious GI adverse events	8 (1.0)	13 (1.3)	4 (0.4)
GI Adverse Events in Patients with Loperamide Rescue Medication use			
System Organ Class Preferred Term	**Eluxadoline 75mg BID (N=272) n (%)**	**Eluxadoline 100mg BID (N=262) n (%)**	**Placebo BID (N=295) n (%)**
Number of subjects with at least 1 GI Adverse Event	93 (34.2)	83 (31.7)	73 (24.7)
Nausea	25 (9.2)	21 (8.0)	15 (5.1)
Constipation	20 (7.4)	23 (8.8)	7 (2.4)
Abdominal pain	15 (5.5)	14 (5.3)	13 (4.4)
GI adverse events leading to discontinuation	11 (4.0)	8 (3.1)	7 (2.4)
Serious GI adverse events	4 (1.5)	4 (1.5)	2 (0.7)

Source: ISS Amendment Tables 2.29, 2.49, and 2.71 and Applicant Response to Information Request dated 30Jan2015

The product label in Section 7 Drug Interactions will state:

Drugs that Cause Constipation	
Clinical Impact:	Increased risk for constipation related adverse reactions and potential for constipation related serious adverse reactions
Intervention:	Avoid use with other drugs that may cause constipation (see below); loperamide may be used occasionally for acute management of severe diarrhea but avoid chronic use. Discontinue loperamide immediately if constipation occurs.
Examples:	alosetron, anticholinergics, opioids

Section 17 Patient Counseling of the label will state: "Instruct patients to not take alosetron with VIBERZI or not take loperamide on a *chronic* basis with VIBERZI due to the potential for constipation. Loperamide may occasionally be used with VIBERZI for *acute management* of severe diarrhea, but must be discontinued if constipation develops. Also, instruct patients to avoid taking VIBERZI with other medications that may cause constipation (for example opioids, anticholinergics, etc.)."

REMS evaluation. The Applicant submitted a risk minimization strategy with the NDA which included a Medication Guide (MG), communication plan and sales force training. The goal was to inform prescribers about the risk of pancreatitis and hepatobiliary sphincter of Oddi (SO) spasm events, and educate them on appropriate patient selection in order to minimize the occurrence of these events. Division of Risk Management (DRISK) in OSE was consulted and they concluded that "risk mitigation measures beyond professional labeling are not warranted for eluxadoline, NDA 206-940… There were no serious or sever safety issues which warrant a boxed warning….Thus, the benefit-risk profile for eluxadoline is acceptable and the risks can be mitigated through professional labeling and a MG.

Summary. I concur with the Clinical reviewers' conclusions that the overall safety profile of eluxadoline is acceptable. GI adverse events (including constipation) were more frequent with eluxadoline than placebo, and sphincter of Oddi dysfunction was observed in the clinical trials, consistent with other drugs in the class. Some of these events were associated with evidence of pancreatitis and/or hepatobiliary events, but they were reversible with discontinuation of drug. They tended to occur early after onset of treatment and it appears that patients with a history of cholecystectomy are at higher risk for these events, which is consistent with other events reported in the literature associated with opioid exposure. These issues will be addressed in labeling. The drug will be contraindicated in patients with:

- Known or suspected biliary duct obstruction; or sphincter of Oddi disease or dysfunction. These patients are at increased risk for sphincter of Oddi spasm.

- Alcoholism, alcohol abuse or alcohol addiction, or in patients who drink more than 3 alcoholic beverages per day. These patients are at increased risk for acute pancreatitis.

- A history of pancreatitis; or structural diseases of the pancreas, including known or suspected pancreatic duct obstruction. These patients are at increased risk for acute pancreatitis.

- Severe hepatic impairment (Child-Pugh Class C). These patients are at risk for significantly increased plasma concentrations of eluxadoline.

- A history of chronic or severe constipation or sequelae from constipation, or known or suspected mechanical gastrointestinal obstruction. These patients may be at risk for severe complications of bowel obstruction.

Sphincter of Oddi Spasm and pancreatitis will be included in the Warnings and Precautions section of the label. The Dosage and Administration section will recommend starting patients at the lower dose level, 75 mg, if they do not have a gallbladder, have mild or moderate hepatic impairment, or are taking concomitant OATP1B1 inhibitors. Section 8.5 Geriatric Use will describe the observation that a higher proportion of patients ≥65 years of age experienced adverse reactions and serious adverse reactions than younger patients.

I agree that no safety issue identified justified a REMS. See Section 5 Clinical Pharmacology for a description of the single safety PMR study that will be included in the approval letter, a renal impairment study.

9. Advisory Committee Meeting

There was no advisory committee meeting to discuss this application. There were no issues identified that required input from an advisory committee.

10. Pediatrics

The applicant submitted a Pediatric Study Plan with the NDA, which included a previously agreed upon iPSP. With the concurrence of PeRC the pediatric study requirement for ages 0 through 5 years will be waived because necessary studies are impossible or highly impracticable. Pediatric studies for ages 6 through 17 years for this application will be deferred because this product is ready for approval for use in adults and the pediatric study have not been completed. The deferred postmarketing pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. They are listed below as they will appear in the approval letter.

2901-1 Conduct a dose ranging study to determine the safety and effectiveness of eluxadoline in pediatric patients 6 through 17 years with diarrhea-predominant irritable bowel syndrome (IBS-D). The pharmacokinetics of eluxadoline in these pediatric patients should also be characterized.

Final Protocol Submission:	06/01/2016
Study Completion:	10/15/2019
Final Report Submission:	01/15/2020

2901-2 Conduct a randomized, double-blind study to determine the safety and effectiveness of eluxadoline in pediatric patients 6 through 17 years with diarrhea-predominant irritable bowel syndrome (IBS-D).

Final Protocol Submission:	03/31/2020
Study Completion:	03/15/2026
Final Report Submission:	06/15/2026

2901-3 Conduct an open-label extension safety study of eluxadoline in pediatric patients 6 through 17 years with diarrhea-predominant irritable bowel syndrome (IBS-D) who participated in the dose ranging (#2901-1) or efficacy (#2901-2) studies.

Final Protocol Submission:	03/31/2020
Study Completion:	03/15/2027
Final Report Submission:	06/15/2027

11. Other Relevant Regulatory Issues

Controlled Substance Staff Review. CSS reviewed the nonclinical and clinical abuse-related data submitted in the application and concluded that eluxadoline has abuse potential. After a meeting with the applicant to discuss CSS's review findings, the applicant submitted revised text for Section 9.0 of the label and proposed that eluxadoline should be placed into Schedule

IV of the Controlled Substances Act (CSA). CSS concurred and recommended eluxadoline's placement into Schedule IV of the Controlled Substances Act. The final decision on scheduling was pending with the Drug Enforcement Agency (DEA) at the time of completion of my review. The label at the time of approval, assuming that a DEA decision remains pending at the PDUFA date for this application, will include "9.1 Controlled Substance *pending*" , and the applicant will be reminded as follows in the approval letter of their agreement not to market eluxadoline without a final DEA scheduling decision:

> "**CONTROLLED SUBSTANCE SCHEDULING**
>
> The final scheduling of this product under the Controlled Substances Act is currently proceeding, but not yet complete as of the date of this letter. We remind you of your signed agreement on Form 356h dated June 26, 2014 and received June 27, 2014 and your agreement on May 20, 2015 not to market this drug until the Drug Enforcement Administration has made a final scheduling decision. We further note that, when the scheduling is finalized, you will need to make appropriate revisions to the package insert, the patient package insert and the carton and immediate-container labels through supplementation of your NDA. This would include the statements detailing the scheduling of Viberzi in the labeling, as required under 21 CFR 201.57(a)(2) and (c)(10)(i)."

CSS reviewed the applicant's evaluation of human physical dependence and concluded that "The human physical dependence study was inadequately designed to evaluate whether chronic administration of eluxadoline produces withdrawal responses indicative of physical dependence." This was only assessed at a single time point in Study 3001, and the assessment tool was limited to SOWS. The applicant proposed language in the label (b) (4) the CSS and Clinical reviewers agreed that this was not appropriate for inclusion in the product label.

Financial Disclosures. The Clinical reviewer reviewed the financial disclosure information submitted in the NDA (refer to Dr. Muldowney's clinical review). She noted that the Applicant provided a single signed copy of FDA Form 3454 with an appended list of investigator names from each covered study. The applicant certified that they had not entered into any financial arrangement with the investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). No investigators reported financial arrangements.

Office of Scientific Investigations (OSI). Site investigations of 5 clinical sites, the CRO (b) (4) and the sponsor (Furiex Pharmaceuticals) were conducted. The final classification for all but two were NAI. Two investigator site investigations were classified VAI. OSI ultimately recommended that the data generated by all of the sites were acceptable in support of the indication. The Clinical reviewer evaluated the findings at the VAI sites and agreed that violations did not adversely affect data integrity. At one of the sites study

personnel had entered data for patients, but corrective action was taken by the investigator. The Clinical reviewer noted that although this violation had the potential to impact data integrity, the enrollment at the site did not represent a significant proportion of the overall study population (8 patients in Study IBS-3001 and 5 patients in Study IBS-3002). In addition, none of the patients enrolled at this site were found to be responders. The Clinical reviewer agreed with OSI's recommendation that data from the inspected sites can be used in support of the NDA.

12. Labeling

See previous sections of this review for specific review issues that were addressed in relevant sections of the label. Key issues included:

- Inclusion of the 75 mg dose in addition to the 100 mg dose
- description of abdominal pain, Sphincter of Oddi dysfunction, pancreatitis, and management of populations at increased risk for these events (See Section 12 Safety of this review)
- labeling for use in patients with hepatic impairment (See Section 5 Clinical Pharmacology of this review)
- how to describe the mechanism of action
- the extent of secondary efficacy analyses that should be included in Section 14 Clinical Studies (see Section 7 Clinical Statistical/Efficacy of this review)
- how to describe potential for withdrawal (see Section 11 Other Relevant Regulatory Issues of this review)
- scheduling (regarding abuse potential) (see Section 11 Other Relevant Regulatory Issues of this review)

Office of Prescription Drug Promotion (OPDP) was consulted to review product labeling and their recommendations were addressed during label review and negotiations.

The Division of Pediatric and Maternal Health was consulted and their label review comments were incorporated in final labeling.

Proprietary name. DMEPA found the applicant's initial proposed proprietary name, (b) (4) unacceptable from a promotional standpoint. DMEPA found the name subsequently proposed in the NDA, (b) (4) acceptable; however, the applicant withdrew that name and submitted another name for review, i.e., "Viberzi". DMEPA found the latter name acceptable.

Medication Guide. Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) conducted a collaborative review of the proposed Medication Guide (MG), and their recommendations were incorporated.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment- The efficacy of eluxadoline has been established for the treatment of IBS-d indication, and the safety risks identified can be managed with product labeling. The risk benefit ratio for this product for the proposed indication is favorable. The only other product currently approved and marketed for this indication has a REMS to address serious safety risks, and it is approved only for treatment of women with IBS-d. Adequate numbers of men were studied in the clinical trials that supported this NDA and there was no justification for limiting eluxadoline's indication to treatment of women.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies – There was no safety risk identified that necessitated restricted distribution or a REMS.

- Recommendation for other Postmarketing Requirements and Commitments – See Section 5 Clinical Pharmacology of this review and the Approval letter for a description of the single PMR safety study, a renal impairment study. See Section 10 Pediatrics of this review and the Approval letter for the pediatric studies that will be required under PREA. Refer to Section 5 Clinical Pharmacology, Section 3 CMC/Biopharmaceutic and the Approval Letter for a description of the PMCs.

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/s/

DONNA J GRIEBEL
05/27/2015