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APPLICATION NUMBER:

206940Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	3/30/2015
From	Ruyi He, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 206940
Applicant	Furiex Pharmaceuticals
Date of Submission	6/26/2014
PDUFA Goal Date	5/25/2015 with 3 months extension (major amendment)
Therapeutic Class	a mixed mu opioid receptor (μOR) agonist and delta opioid receptor (δOR) antagonist
Proprietary Name / Established (USAN) names	TBD (eluxadoline) tablets
Proposed Indication(s)	Trade name (eluxadoline) is indicated for the treatment of diarrhea and abdominal pain in men and women with diarrhea predominant irritable bowel syndrome (IBS-d).
Proposed Dosage forms / Strength	100 mg (100 mg eluxadoline tablet)
Recommended:	I recommend that NDA 206940 for TRADENAME (eluxadoline) tablets be approved in adults for the treatment of irritable bowel syndrome with diarrhea predominant (IBS-d).

1. Introduction

Eluxadoline is a mixed mu opioid receptor (μOR) agonist/delta opioid receptor (δOR) antagonist with low oral bioavailability with a proposed indication for the treatment of diarrhea predominant irritable bowel syndrome (IBS-d). According to the sponsor, the beneficial effects of eluxadoline at the proposed dose of 100 mg twice daily in treating IBS-d arise via local action within the gastrointestinal tract, where the extensive expression of opioid receptors plays a key role in regulating gastrointestinal motility, secretion, and visceral sensation. While the locally acting μOR agonist loperamide is effective in treating diarrhea, it has limited effectiveness in IBS-d on abdominal pain and the possibility for constipation (Scand J Gastroenterol. 1996 May;31(5):463-8. A double-blind placebo-controlled trial with loperamide

in irritable bowel syndrome; Efskind PS et al; World J Gastroenterol. 2005 Mar 14;11(10):1540-3; A blind, randomized comparison of racecadotril and loperamide for stopping acute diarrhea in adults. Wang HH et al). By contrast, the sponsor proposed that the mixed opioid pharmacology of eluxadoline may have the ability to effectively improve abdominal pain and stool consistency in IBS-d patients while mitigating the risk of constipation.

2. Background

Irritable bowel syndrome (IBS) is a functional bowel disorder affecting up to 20% of adolescents and adults in North America, with a higher prevalence in women. The diagnosis of IBS is based on the symptom-based Rome III criteria. Diarrhea predominant IBS accounts for approximately one-third of all cases of IBS and is defined as IBS with loose or watery stools with ≥25% of bowel movements.

The pathophysiology of IBS is complex and remains uncertain. The symptoms of IBS are believed to relate to a number of physiological factors including colonic dysmotility, enhanced visceral hypersensitivity, altered mucosal immune and inflammatory function (including changes in bacterial flora), and dysregulation of intestinal motor sensory, and CNS function (brain-gut dysfunction). Finally, psychosocial factors including daily stress may impact the manifestation of IBS related symptoms.

IBS chronic relapsing nature has been shown to have a significant impact on patient quality of life and day-to-day functioning. IBS has been shown to impact not only an individual's physical symptoms, but emotional and social functions as well. IBS is associated with significant direct and indirect medical expenses, as well as increased indirect costs to patients and the community through work absenteeism.

The current treatment options for IBS-D are limited. There are currently no unrestricted prescription products on the market indicated for the treatment of IBS-D. Alosetron, a selective serotonin 5-HT3 receptor antagonist, is the only product approved for use in IBS-d in the US; however, it is approved only for women and under restricted distribution due to safety concerns related to severe constipation and ischemic colitis. Loperamide, a peripherally restricted μOR agonist, is a frequently used antidiarrheal , but it has not been shown to have significant effectiveness in managing the abdominal pain associated with IBS-D, and it is associated with treatment related constipation. Bile acid binders including cholestyeramine and colesevelam may provide some relief of diarrhea symptoms when associated with bile acid malabsorption, and antidepressants are frequently employed, not only for treatment of associated depression, but for their neuromodulatory and analgesic properties as well. There is a need for additional treatment options in IBS-d that improve both diarrhea and abdominal pain and discomfort, without significant adverse effects.

The FDA published guidance for industry in 2012 to assist the pharmaceutical industry who is developing drugs for the treatment of IBS. Important concepts from this guidance included a recommendation for a primary endpoint that measures the effect of treatment on two major IBS

signs and symptoms, abnormal defecation and abdominal pain, with the primary analysis comparing the response rates between the investigational drug and placebo.

Summary of Presubmission Regulatory Activity Related to Submission

Table 1 below summarizes pre-submission regulatory meetings and correspondence. A more detailed account of meetings and agreements is provided in Appendix 5 in Dr. Muldowney's review.

Table 1: Pre-Submission Regulatory History for NDA 206940

Date	Regulatory Action(s)
21 November 2007	IND 79,214 submission for JNJ-27018966 for IBS-d
16 March 2010	EOP1 meeting and discussion of Phase 2 POC study
08 July 2010	Advice letter to sponsor regarding abuse potential study requirements
19 January 2011	Fast track designation granted
05 July 2011	Type C meeting to discuss interim analysis results from phase 2 study and discuss proposed endpoints for phase 3 studies
27 September 2011	Type B EOP2 meeting, agreement reached on overall Phase 3 study design (primary endpoints, responder definitions, safety exposures)
24 January 2012	Type C EOP2 CMC meeting to discuss the CMC development program
22 May 2012	Advice letter to sponsor waiving IRB requirements for the use of JNJ-27018966 in a foreign investigational study and providing statistics recommendations for phase 3 protocols
11 June 2012	Advice letter to sponsor agreeing that renal impairment study could be performed after NDA submission and approval and agreeing on general eligibility criteria
13 June 2012	Advice letter to sponsor providing agreement on the submitted protocols IBS-3001 and -3002 and confirming that finalization of the IBS guidance will not impact the Agency's acceptance of the protocols.
06 December 2012	Type C meeting, written response only, providing recommendations for assessing the abuse liability of eluxadoline and confirming that an IV human abuse potential study should not be performed.
02 November 2012	Advice letter to sponsor that the Agency did not agree with (b) (4) thorough QTc study and recommends a single dose study.
15 October 2013	Type C Meeting to discuss proposed PSP
31 January 2014	Type C meeting, written responses only providing agreement with the planned analyses in support of ISS and ISE
25 February 2014	Type B, Pre-NDA, CMC meeting to discuss the Quality section of the NDA submission
22 April 2014 (with follow-up correspondence 08 May 2014)	Type B, Pre-NDA meeting to discuss the NDA submission. The Agency agreed the NDA could be submitted based on complete efficacy data and available safety data as of 24 January 2014. The remaining safety data can be provided as a major safety amendment.

Source: Dr. Laurie Muldowney's review.

IND 79,214 was submitted on November 21, 2007 and received fast track designation in the treatment of IBS-d on January 19, 2011. Presubmission regulatory activities related to this submission included approximately 8 formal face-to-face meetings between the Sponsor and

FDA. In addition, there were a number of teleconferences and written correspondences exchanged during the development program. The Phase 3 protocols were developed in communication with the FDA and are consistent with the overall recommendations of the final IBS guidance, including the general study design, patient population, and primary efficacy endpoint. In order to support global registration, the Sponsor included an evaluation of efficacy at 12 weeks (FDA recommendation) and 26 weeks (EMA recommendation). In addition, there were multiple interactions between the Sponsor and the FDA's Controlled Substance Staff regarding abuse potential study requirements.

3. CMC/Device

Dr. Yichun Sun, the CMC reviewer, has determined that the applicant has provided sufficient information to assure identity, strength, purity, and quality of the drug product. The Office of Compliance has made an overall 'acceptable' recommendation for the facilities involved in this application.

Drug Substance
The active ingredient is eluxadoline (b) (4) and is a white crystalline powder. It has a melting point of 189.4°C. Its solubility is pH dependent. It is soluble in 0.1 N HCl. It is slightly soluble in pH 4 citrate buffer. It is slightly soluble in water. It is sparingly soluble in pH 10 borate buffer. It is freely soluble in 0.1N NaOH.

Drug Product
It is available as 75 mg and 100 mg tablets for oral administration. The 75 mg tablets are capsule-shaped, coated in pale-yellow to light tan color and debossed with "FX75" on one side.

The 100 mg tablets are capsule-shaped, coated, pink-orange to peach color, and debossed with "FX100" on one side. In addition to the active ingredient, eluxadoline, each tablet contains the following inactive ingredients: silicified microcrystalline cellulose, silicon dioxide, crospovidone, mannitol, magnesium stearate and Opadry II. (b) (4) The manufacturing process of the tablets includes (b) (4) Process parameters are defined and controlled during the tablet manufacturing process. The tablets (60 counts) are packaged in white (b) (4) opaque high density polyethylene (HDPE) bottles with (b) (4) screw caps (b) (4). The proposed expiration dating period of 24 months is supported by the primary and supportive stability data.

Dr. Sun has following recommendation on Phase 4 (Post-Marketing) Commitments, or Agreements:
The applicant needs to re-evaluate the dissolution acceptance criterion after dissolution data from at least 30 lots of commercial drug products are available, or a maximum period of 1 year post-launch. Additionally, a 15 minute time-point will be added to the dissolution test at time of product release and in the stability protocol where profiles will be followed at 10, 15, 20 and

30 minutes. The final evaluation will include an assessment of whether the dissolution criterion of Q = (b) (4)% can be applied at 10-minutes or 15- minutes, instead of the 20-minute interval. Please see Yichun Sun's review dated March 4, 2015 in detail.

Dr. Assadollah Noory, ONDP-Biopharmaceutics reviewer, completed the review of the Biopharmaceutics portion of this NDA. The Division of Biopharmaceutics recommends approval of NDA 206940 and concurred with Dr. Sun's Phase 4 commitment. Based on Dr. Noory, the Sponsor's proposed dissolution acceptance criterion of Q= (b) (4)% at 20 min is accepted as the interim product release and quality control criterion. The Division of Biopharmaceutics discussed the recommendation for Phase 4 study with the sponsor and the sponsor committed on Feb. 09, 2015 to do so.

4. Nonclinical Pharmacology/Toxicology

Dr. Tamal Chakraborti is the reviewer and Dr. Sushanta Chakder is the team leader for this NDA and they concluded in the review that from a nonclinical standpoint, this NDA is recommended for approval and they have no recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps.

Based on the Dr. Chakraborti's review, eluxadoline has been shown to be a μOR agonist and δOR antagonist, with moderate kappa OR (κOR) agonist activity. In animal efficacy studies, eluxadoline has shown efficacy in normalizing GI transit and defecation in several animal models of altered GI function induced by stress, castor-oil or GI inflammation.

In anesthetized dogs, eluxadoline did not show any significant cardiovascular effect up to an IV cumulative dose of 1.443 mg/kg (124 times the Cmax in humans at the 100 mg dose). In conscious telemetered monkeys, QT and QTc intervals were slightly prolonged (106% to 112%) at SC doses of 5, 15 and 30 mg/kg. In a respiratory safety pharmacology study in rats at IV doses of 5, 10 and 20 mg/kg, depressive changes in breathing, consistent with μOR agonists, were observed. No significant safety signals were identified in the CNS safety pharmacology studies in rats up to an oral dose of 300 mg/kg.

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).

5. Clinical Pharmacology/Biopharmaceutics

Dr. Dilara Jappar is the Clinical Pharmacology reviewer for this NDA and Dr. Sue Chih Lee is the Team Leader. They concluded that the Office of Clinical Pharmacology has found the submission acceptable from a clinical pharmacology standpoint. They do have several recommendations on Phase 4 (Post-Marketing) Commitments or Agreements that are listed in the section 13 of this review.

Dr. Jappar provided the following summary based on her review of this NDA.

Dose-Response Relationship and Dose Selection
The phase 2 dose-ranging study assessed 5 mg, 25 mg, 100 mg, and 200 mg BID dosing regimens vs. placebo in IBS-d patients. Using the primary efficacy analysis consistent with that recommended in the current IBS guidance, the 5 mg and 25 mg BID doses were not efficacious while 100 mg and 200 mg doses had similar response rate. However, the 200 mg BID regimen was associated with a increased rate of treatment related AEs, discontinuation rate, and GI related AE (most commonly reported AE). Therefore, 100 mg BID dose was carried into Phase 3 studies.

QTc Prolongation Potential: The QT-IRT review team concluded that no significant QTc prolongation was observed when 100 mg and 1000 mg (supra therapeutic dose) of eluxadoline was administered to healthy subjects.

Pharmacokinetics:
Eluxadoline has a dose proportional increase in C_{max} and slightly less than dose proportional increase in AUC. PK variability of eluxadoline was relatively high (51-98%). Daily BID dosing results in no evidence of accumulation.

Absorption: After single dose administration of 100 mg eluxadoline in healthy subjects, the peak plasma concentration was reached in about 2 hours with C_{max} of approximately 2-4 ng/mL. High fat meal increased eluxadoline C_{max} by 50% and AUC by 60% at the 100 mg dose. Because phase III trials were conducted under fed conditions, the label recommends taking eluxadoline with food. Absolute bioavailability of eluxadoline was not evaluated.

Distribution: The plasma protein binding was approximately 81% between concentrations of 200-5700 ng/mL.

Metabolism: Metabolism of eluxadoline is not clearly established. In the phase 2/3 studies, it was noted that patients who took strong CYP inhibitors with eluxadoline concomitantly had higher AEs (e.g., 97.3% vs. 52.6%) and SAEs (e.g., 17.3% vs. 3%) compared to subject who were on eluxadoline only. Dr. Jappar recommends that the sponsor conduct further *in-vitro* studies to characterize the metabolism of eluxadoline as a PMC. In the meantime until further data become available, she recommends to avoid concomitant use of strong CYP inhibitors with eluxadoline if possible; If not, monitor for adverse reactions related to eluxadoline. I concur with her recommendation.

Elimination: The terminal half-life of eluxadoline across various 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. From various studies in healthy subjects, the mean fraction of oral dose of eluxadoline excreted as unchanged drug in urine was less than 0.17 %.

Specific Populations:
Gender: The exposure of eluxadoline is 35 % higher in females than in males. No dose adjustment is needed based on gender.

Hepatic Impairment: In patients with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment, the exposure is 6- fold higher in AUC and 4-fold higher in C_{max} than the exposure in subjects with normal hepatic function. AUC and C_{max} in patients with severe (Child-Pugh Class C) hepatic impairment are about 16-fold and 19-fold higher than that of in subjects with normal hepatic function, respectively. The sponsor proposed to contraindicate eluxadoline in patients with hepatic impairment due to cirrhosis. However due to the difference in the level of change in systemic exposure of eluxadoline, clinical pharmacology team proposes to only contraindicate eluxadoline in patients with severe hepatic impairment and avoid the use of eluxadoline in patients with mild and moderate hepatic impairment if possible; If not, monitor for adverse reactions related to eluxadoline when eluxadoline is used in patients with mild and moderate hepatic impairment. We discussed this issue during the team meeting and team agreed.

Renal Impairment: There was no dedicated PK study to evaluate the effect of renal impairment on PK of eluxadoline. In the phase 3 studies, the % of patients with AEs were comparable between the patients with mild renal impairment and the overall population. In addition, in patients with mild renal impairment, the % patients with AEs were comparable for subjects who were treated with 75 mg or 100 mg eluxadoline vs. placebo. However, there is not an adequate number of subjects with moderate renal impairment to draw any conclusion (n=6). Therefore, I agreed that a renal impairment study will be required as a post-marketing study as a PMC.

Based on sponsor's population PK analysis, age (within the range of 18 to 65 years old), race, body weight and BMI had no impact on eluxadoline PK.

In-vitro Drug-Drug Interaction Evaluation :

CYP Inhibition: In an *in-vitro* study, eluxadoline appears to show time-dependent inhibition of CYP3A4 at 50 μM, a concentration that can be achieved in the gut (I_{gut} is estimated to be 700 μM). Further *in-vitro* studies are necessary to assess the *in-vivo* relevance of this potential time-dependent inhibition of CYP3A4 by eluxadoline. Therefore, in the meantime until further data become available, the label will state "monitor the systemic level of narrow therapeutic index drugs that are CYP3A4 substrates when a concomitant use with eluxadoline is initiated or discontinued". Eluxadoline up to 50 μM concentration did not show time-dependent inhibition toward CYP1A2, 2C9, 2C19 and 2D6.

In-vivo drug interactions:
Effect of other drugs on the PK of eluxadoline
Cyclosporine: Coadministration of single oral dose of 600 mg cyclosporine (an inhibitor of many transporters including OATP1B1 and MRP2) with single oral dose of 100 mg eluxadoline increased eluxadoline AUC by 4.4 fold and C_{max} by 6.2 fold. The sponsor proposed to monitor patients for adverse reaction when eluxadoline is prescribed concomitantly with OATP1B1 inhibitors in the proposed label. Clinical pharmacology team recommends that patients to avoid concomitant use of OATP1B1 inhibitors with eluxadoline if possible; if not, monitor for adverse reactions related to eluxadoline. The team discussed this issue and agreed this proposal.

Please see Dr. Jappar's full review in details.

6. Clinical Microbiology

NA

7. Clinical/Statistical- Efficacy

Dr. Yeh-Fong Chen is the statistical reviewer for this NDA and Dr. Mike Welch concurred with her conclusion.

Dr. Chen concluded in her review that the sponsor submitted two phase 3 studies to demonstrate the efficacy of eluxadoline as a treatment for abdominal pain and diarrhea in adult patients with diarrhea predominant irritable bowel syndrome (IBS-d). For both studies, the 75 mg and 100 mg doses of eluxadoline showed a statistically significant difference in the primary endpoint, composite response, compared with placebo at 12 weeks.

Components of the primary endpoint, abdominal pain response and stool consistency response were specified as secondary endpoints. For both studies and both doses, only stool consistency response indicated a significant difference compared to placebo at 12 weeks; no statistical differences were shown for abdominal pain response. As the sponsor did not pre-specify a multiplicity adjustment procedure for type I error control for secondary endpoints, formal hypothesis testing would not be appropriate. However, Dr. Chen indicated in her review that the pain and stool consistency responder results and/or scores may be clinically informative and can augment labeling provided these results are presented with descriptive statistics only.

To further assess eluxadoline's effect on reducing patients' abdominal pain, Dr. Chen, the statistical reviewer, performed a mixed effects model for repeated measures (MMRM) analysis on patients' pain scores directly. Based on this exploratory analysis, both doses of eluxadoline appeared to show treatment benefit in treating patients' diarrhea and in reducing their abdominal pain. For detailed analysis, please see Dr. Chen's full review dated on March 7, 2015.

The efficacy of eluxadoline for the treatment of IBS-d was initially evaluated in a Phase 2, dose-ranging study and subsequently confirmed in two Phase 3 studies.

The clinical development program was conducted in parallel with evolving regulatory guidance in the United States (US) and European Union (EU) with respect to the evaluation of products for IBS. While the pre-specified efficacy endpoints in the Phase 2 study differed from the current recommendations of both the Food and Drug Administration (FDA) and European Medicines Agency (EMA), results from the *post hoc* analyses of that study formed the basis for the endpoints evaluated in the subsequent Phase 3 studies.

The Phase 2, dose-ranging study (Study IBS-2001) was conducted to evaluate the clinical response relative to placebo of different doses of eluxadoline (5 mg twice daily [BID], 25 mg BID, 100 mg BID, and 200 mg BID) in patients diagnosed with IBS with a subtype of diarrhea by the Rome III criteria. Study IBS-2001 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study that consisted of a 12-week double-blind treatment period and a 2-week follow-up period.

This study demonstrated that patients with IBS-d who were treated with 100 mg BID and 200 mg BID eluxadoline were twice as likely as placebo patients to achieve study response based upon a *post hoc* analysis that evaluated efficacy data over all 12 weeks of double-blind treatment (study response was defined as meeting the composite endpoint of prespecified improvements in both worst abdominal pain and stool consistency on the same day for at least 50% of time on the study).

Despite the fact that the 200-mg BID dose also demonstrated statistically significant superiority over placebo in the multiple analyses used to explore the Phase 2 data, increasing the dose failed to improve the *post hoc* response rates over the 100-mg BID dose. Moreover, the frequency of adverse events (AEs) at 200 mg BID, particularly gastrointestinal AEs, prompted Furiex to choose 100 mg BID as the top dose from the Phase 2 study to carry into the Phase 3 program. Although the efficacy of 75 mg BID was not specifically explored in the Phase 2 study, this dose was included as one of the therapeutic arms in the Phase 3 studies based on efficacy trends and the favorable safety profile of doses up to 100 mg BID.

The Phase 3 protocols were developed based upon discussions with the FDA and in parallel to finalization of the FDA guidance in May 2012. The studies are therefore consistent with the overall recommendations of the final IBS guidance, including the general study design, the patient population, and the primary efficacy endpoint. The Phase 3 studies were also designed

to support global registration of eluxadoline and therefore include additional considerations for the EMA, in particular the evaluation of efficacy over 26 weeks.

Both Phase 3 studies were multicenter, randomized, double-blind, placebo-controlled, parallel-group studies comparing 2 doses of eluxadoline (75 mg BID and 100 mg BID) with placebo in patients diagnosed with IBS with a subtype of diarrhea by the Rome III criteria.

Study IBS-3001 included a 52-week double-blind treatment period and a 2-week post-treatment follow-up period. Study IBS-3002 included a 26-week double-blind treatment period and a 4-week, single-blind withdrawal period.

In both Phase 3 studies, the primary analysis was conducted using a 12-week composite responder endpoint. This primary endpoint was consistent with the guidance provided by the FDA in May 2012. In addition, the proportion of composite responders over Weeks 1-26 was also evaluated to meet the EMA requirements and is presented in this summary as well.

Symptoms of IBS-d (eg, abdominal pain, stool consistency, abdominal discomfort, abdominal bloating, IBS-d global symptoms, and bowel functioning) and loperamide rescue medication use were collected in an electronic diary daily for 26 weeks in Study IBS-3001 and daily for 30 weeks in Study IBS-3002.

Composite Responders:
The primary efficacy endpoint was the composite responder proportion evaluated over the initial 12 weeks of double-blind treatment for the FDA and over the initial 26 weeks of treatment for the European Medicines Agency (EMA). Responder rates were compared based on patients who met the daily composite response criteria (pain and stool consistency) for at least 50% of the days with diary entries from Weeks 1-12 and Weeks 1-26. A patient must have met BOTH of the following criteria on any given day to be a daily responder with no use of rescue medication:
• Daily pain response: worst abdominal pain scores in the past 24 hours improved by ≥30% compared to baseline pain (average of week prior to randomization)
• Daily stool consistency response: BSS score <5 or the absence of a bowel movement

To be eligible to be a composite responder, a patient must have had a minimum of 60 days of diary entries over Weeks 1-12 and a minimum of 110 days of diary entries over Weeks 1-26.

Pain Responders:
A responder was defined as a patient who met the daily pain response criterion (as described above for composite response) for at least 50% of the days over each interval.

Stool Consistency Responders:
A stool consistency responder was defined as a patient who met the stool consistency response criteria (as described above for composite response) for at least 50% of the days over each interval.

To be eligible to be a pain responder or stool consistency responder, a patient must have had a minimum of 60 days of diary entries over Weeks 1-12 and a minimum of 110 days of diary entries over Weeks 1-26.

For each of the eluxadoline dose groups (75 mg BID and 100 mg BID), the proportion of composite responders over Weeks 1-12 and Weeks 1-26 was compared to the proportion of composite responders in the placebo group using pairwise Cochran-Mantel-Haenszel (CMH) tests comparing active treatment groups to placebo for each interval.

Study IBS-3001

Study IBS-3001 is a Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to evaluate the efficacy and safety of orally administered eluxadoline (75 mg BID and 100 mg BID) in patients with IBS-d in the US, Canada, and the United Kingdom (UK). The study consisted of a pretreatment period (consisting of an up to 1-week prescreening period and an up to 3-week screening period), a 52-week double-blind treatment period (which included 26 weeks of efficacy [via electronic diary] and safety assessments followed by 26 weeks of double-blind safety assessments), and a 2-week posttreatment follow-up period. An electronic diary was used during the screening period (to determine patient eligibility) and the first 26 weeks of the double-blind treatment period.

A total of 444 men and 838 women (18 to 80 years of age) with IBS-d met the screening and Baseline criteria for pain (average of daily worst abdominal pain scores >3.0 [scale 0-10] during the week prior to randomization), stool consistency (average BSS score of ≥5.5 [scale 1-7] and at least 5 days with a BSS score ≥5 during the week prior to randomization), and were enrolled and randomized to one of the following 3 treatment groups: placebo or eluxadoline at doses of 75 or 100 mg BID. The stool consistency requirement ensured that patients had at least 2 days within the week prior to randomization with a BSS score of 6, in accordance with the final FDA IBS guidance.

Patients were instructed to take their study drug twice daily (in the morning and evening) with food. During the double-blind treatment period, patients were allowed to take loperamide rescue medication for the acute treatment of uncontrolled diarrhea, but were not allowed to take any other antidiarrheal, antispasmodic agent, or rifaximin.

Efficacy was assessed during the first 26 weeks of double-blind treatment based primarily on patient reports of daily worst abdominal pain and daily stool consistency.

The safety of eluxadoline was assessed based primarily on AEs, clinical laboratory test results, and 12-lead ECGs.

Efficacy results:
The efficacy of eluxadoline was assessed using a composite responder analysis as defined above.

Table 2 CMH Analysis of Composite Responders in Study IBS-3001 (ITT Analysis Set)

Interval Treatment	Number (%)		*P* value[a]
	Responder	Non-Responder	
Weeks 1-12 (FDA primary endpoint)			
Eluxadoline 75 mg BID (N=427)	102 (23.9)	325 (76.1)	0.014
Eluxadoline 100 mg BID (N=426)	107 (25.1)	319 (74.9)	0.004
Placebo BID (N=427)	73 (17.1)	354 (82.9)	--
Weeks 1-26 (EMA primary endpoint)			
Eluxadoline 75 mg BID (N=427)	100 (23.4)	327 (76.6)	0.112
Eluxadoline 100 mg BID (N=426)	125 (29.3)	301 (70.7)	<0.001
Placebo BID (N=427)	81 (19.0)	346 (81.0)	--

Abbreviations: BID = twice daily; EMA = European Medicines Agency; FDA = Food and Drug Administration; ITT = intent to treat

Source: Study IBS-3001 CSR Table 11-6

The primary endpoint analysis was based on composite responders looking at both daily pain response and daily stool consistency response. This is consistent with recommendations in FDA guidance on the clinical evaluation of drugs for treatment of IBS. A significantly higher proportion of patients in the eluxadoline 100mg BID arm were composite responders compared to the placebo arm (25.1% vs 17.1%, p = 0.004) over Weeks 1 – 12 of treatment. Similar results were seen with the 75 mg group compared to placebo over the first 12 weeks of treatment.

The proportion of composite responders was analyzed over 4-week intervals. Table 3 presents results from the CMH analysis of composite responders by interval. The proportion of composite responders was higher in both eluxadoline treatment groups compared to placebo for each of the 4-week intervals.

Table 3: CMH Analysis of Composite Responders by Interval (Daily Response Criteria; ITT Analysis Set)

Interval Treatment	Number (%) Responder	 Non-Responder	 *P* value[a]
Weeks 1-4			
Eluxadoline 75 mg BID (N=427)	88 (20.6)	339 (79.4)	0.003
Eluxadoline 100 mg BID (N=426)	96 (22.5)	330 (77.5)	<0.001
Placebo BID (N=427)	55 (12.9)	372 (87.1)	--
Weeks 5-8			
Eluxadoline 75 mg BID (N=427)	113 (26.5)	314 (73.5)	0.023
Eluxadoline 100 mg BID (N=426)	123 (28.9)	303 (71.1)	0.002
Placebo BID (N=427)	85 (19.9)	342 (80.1)	--
Weeks 9-12			
Eluxadoline 75 mg BID (N=427)	101 (23.7)	326 (76.3)	0.514
Eluxadoline 100 mg BID (N=426)	129 (30.3)	297 (69.7)	0.005
Placebo BID (N=427)	93 (21.8)	334 (78.2)	--
Weeks 13-16			
Eluxadoline 75 mg BID (N=427)	97 (22.7)	330 (77.3)	0.563
Eluxadoline 100 mg BID (N=426)	124 (29.1)	302 (70.9)	0.007
Placebo BID (N=427)	90 (21.1)	337 (78.9)	--
Weeks 17-20			
Eluxadoline 75 mg BID (N=427)	118 (27.6)	309 (72.4)	0.047
Eluxadoline 100 mg BID (N=426)	123 (28.9)	303 (71.1)	0.017
Placebo BID (N=427)	93 (21.8)	334 (78.2)	--
Weeks 21-24			
Eluxadoline 75 mg BID (N=427)	117 (27.4)	310 (72.6)	0.016
Eluxadoline 100 mg BID (N=426)	120 (28.2)	306 (71.8)	0.008
Placebo BID (N=427)	87 (20.4)	340 (79.6)	--

Pain Responders

Table 4 presents results from the CMH analysis of pain responders (individual pain component of the daily composite responder definition) over the intervals from Weeks 1-12 and Weeks 1-26. The proportion of pain responders for the 75-mg and 100-mg treatment groups was higher than placebo over the 3-month interval (Weeks 1-12) and the 6-month interval (Weeks 1-26); however, these differences were not statistically significant ($P > 0.05$).

Table 4: CMH Analysis of Pain Responders (Daily Response Criterion; ITT Analysis Set)

Interval / Treatment	Number (%)		*P* value[a]
	Responder	Non-Responder	
Weeks 1-12			
Eluxadoline 75 mg BID (N=427)	181 (42.4)	246 (57.6)	0.404
Eluxadoline 100 mg BID (N=426)	184 (43.2)	242 (56.8)	0.284
Placebo BID (N=427)	169 (39.6)	258 (60.4)	
Weeks 1-26			
Eluxadoline 75 mg BID (N=427)	193 (45.2)	234 (54.8)	0.582
Eluxadoline 100 mg BID (N=426)	198 (46.5)	228 (53.5)	0.355
Placebo BID (N=427)	185 (43.3)	242 (56.7)	

Abbreviations: BID = twice daily; CMH = Cochran-Mantel-Haenszel; ITT = intent to treat

[a] P value is based on Chi-square test

Pain responder = a patient who met the daily pain response criterion on at least 50% of days during the interval and for the 12-week interval had a minimum of 60 days of diary data from Weeks 1-12 OR for the 26-week interval had a minimum of 110 days of diary data from Weeks 1-26

Daily pain response = worst abdominal pain score in the past 24 hours improved by ≥30% compared to baseline pain

Source: Tables 14.2.2.4.7 and 14.2.2.2.1

To further assess eluxadoline's effect on reducing patients' abdominal pain, Dr. Chen, the statistical reviewer, performed a mixed effects model for repeated measures (MMRM) analysis on patients' pain scores directly. Based on this exploratory analysis, both doses of eluxadoline appeared to show treatment benefit in treating patients' diarrhea and in reducing their abdominal pain. For detail analysis, please see Dr. Chen's full review dated on March 7, 2015.

Stool Consistency (BSS) Responders

Table 5 presents results from the CMH analysis of stool consistency responders (individual stool consistency component of the daily composite responder definition) over the intervals from Weeks 1-12 and Weeks 1-26. The proportion of stool consistency responders was higher than that of placebo for the 100-mg treatment group over the 3-month interval (Weeks 1-12) and the 6-month interval (Weeks 1-26) and was higher than placebo for the 75-mg treatment group over the 3-month interval
(Weeks 1-12).

Table 5 CMH Analysis of Stool Consistency Responders (Daily Response Criterion)

Interval Treatment	Number (%)		*P* value[a]
	Responder	Non-Responder	
Weeks 1-12			
Eluxadoline 75 mg BID (N=427)	128 (30.0)	299 (70.0)	0.008
Eluxadoline 100 mg BID (N=426)	146 (34.3)	280 (65.7)	<0.001
Placebo BID (N=427)	94 (22.0)	333 (78.0)	--
Weeks 1-26			
Eluxadoline 75 mg BID (N=427)	120 (28.1)	307 (71.9)	0.186
Eluxadoline 100 mg BID (N=426)	145 (34.0)	281 (66.0)	0.001
Placebo BID (N=427)	103 (24.1)	324 (75.9)	--

Abbreviations: BID = twice daily; BSS = Bristol Stool Scale; CMH = Cochran-Mantel-Haenszel; ITT = intent to treat

[a] P value is based on Chi-square test

Stool consistency responder = a patient who met the daily stool consistency response criterion on at least 50% of days during the interval and for the 12-week interval had a minimum of 60 days of diary data from Weeks 1-12 OR for the 26-week interval had a minimum of 110 days of diary data from Weeks 1-26

Daily stool consistency response = BSS score <5, or a diary entry reporting the absence of a bowel movement if accompanied by ≥30% improvement in worst abdominal pain compared to baseline pain

Source: Tables 14.2.2.5.6 and 14.2.2.5.8b

Results from the exploratory analyses of stool consistency responders using the logistic regression model over Weeks 1-12 and Weeks 1-26 were consistent with the findings from the CMH analysis.

I concurred with Dr. Muldowney that the efficacy data from Study 3001 support both 75mg and 100mg in patients with IBS-D.

Study IBS-3002

Study-3002 is a randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of orally administered eluxadoline (75 mg BID and 100 mg BID) in patients with IBS-d in the US, Canada, and the UK. The study consisted of a pretreatment period (consisting of an up to 1-week prescreening period and an up to 3-week screening period), a 26-week double-blind treatment period, and a 4-week single-blinded withdrawal period. An electronic diary was used during the screening period (to determine eligibility) and during the full 30 weeks of blinded treatment.

A total of 378 men and 768 women (18 to 77 years of age) with IBS-d met the screening and Baseline criteria for pain (average of daily worst abdominal pain scores >3.0 [scale 0-10] during the week prior to randomization), stool consistency (average BSS score of ≥5.5 [scale 1-7] and were enrolled and randomized to one of the following 3 treatment groups: placebo or eluxadoline at doses of 75 or 100 mg BID. The stool consistency requirement ensured that patients had at least 2 days within the week prior to randomization with a BSS score of 6, in accordance with the final FDA guidance. This study design is same as Study 3001.

Patients were instructed to take their study drug twice daily (in the morning and evening) with food. During the double-blind treatment period and single-blind withdrawal period, patients were allowed to take loperamide rescue medication for the acute treatment of uncontrolled diarrhea, but were not allowed to take any other antidiarrheal, antispasmodic agent, or rifaximin.

Efficacy was assessed during the 26-week double-blind treatment period based primarily on patient reports of daily worst abdominal pain and daily stool consistency.

Efficacy results:
The efficacy of eluxadoline was assessed using a composite responder analysis as defined above.

Applying a Bonferroni adjustment for multiple comparisons, the proportion of composite responders for both the 75-mg and 100-mg treatment groups was statistically superior to placebo over Weeks 1-12 (P <0.001) and Weeks 1-26 (P ≤0.001).

Table 6: CMH Analysis of Composite Responders in Study IBS-3002 (ITT Analysis Set)

Interval Treatment	Number (%) Responder	 Non-Responder	 *P* value[a]
Weeks 1-12 (FDA primary endpoint)			
Eluxadoline 75 mg BID (N=381)	110 (28.9)	271 (71.1)	<0.001
Eluxadoline 100 mg BID (N=382)	113 (29.6)	269 (70.4)	<0.001
Placebo BID (N=382)	62 (16.2)	320 (83.8)	--
Weeks 1-26 (EMA primary endpoint)			
Eluxadoline 75 mg BID (N=381)	116 (30.4)	265 (69.6)	0.001
Eluxadoline 100 mg BID (N=382)	125 (32.7)	257 (67.3)	<0.001
Placebo BID (N=382)	77 (20.2)	305 (79.8)	--

Abbreviations: BID = twice daily; EMA = European Medicines Agency; FDA = Food and Drug Administration; ITT = intent to treat

Source: Study IBS-3002 CSR Table 11-6

For both treatment groups, significance over placebo for composite response was demonstrated over the initial 4 weeks of treatment (Weeks 1-4) and was also demonstrated over the latter 4-week intervals (Weeks 17-20 and Weeks 21-24).

Table 7 CMH Analysis of Composite Responders by Interval (Daily Response)

Interval Treatment	Number (%)		
	Responder	Non-Responder	*P* value[a]
Weeks 1-4			
Eluxadoline 75 mg BID (N=381)	96 (25.2)	285 (74.8)	<0.001
Eluxadoline 100 mg BID (N=382)	102 (26.7)	280 (73.3)	<0.001
Placebo BID (N=382)	46 (12.0)	336 (88.0)	--
Weeks 5-8			
Eluxadoline 75 mg BID (N=381)	120 (31.5)	261 (68.5)	<0.001
Eluxadoline 100 mg BID (N=382)	128 (33.5)	254 (66.5)	<0.001
Placebo BID (N=382)	76 (19.9)	306 (80.1)	--
Weeks 9-12			
Eluxadoline 75 mg BID (N=381)	123 (32.3)	258 (67.7)	0.001
Eluxadoline 100 mg BID (N=382)	122 (31.9)	260 (68.1)	0.002
Placebo BID (N=382)	84 (22.0)	298 (78.0)	--
Weeks 13-16			
Eluxadoline 75 mg BID (N=381)	117 (30.7)	264 (69.3)	0.002
Eluxadoline 100 mg BID (N=382)	129 (33.8)	253 (66.2)	<0.001
Placebo BID (N=382)	80 (20.9)	302 (79.1)	--
Weeks 17-20			
Eluxadoline 75 mg BID (N=381)	119 (31.2)	262 (68.8)	0.007
Eluxadoline 100 mg BID (N=382)	119 (31.2)	263 (68.8)	0.007
Placebo BID (N=382)	86 (22.5)	296 (77.5)	
Weeks 21-24			
Eluxadoline 75 mg BID (N=381)	110 (28.9)	271 (71.1)	0.004
Eluxadoline 100 mg BID (N=382)	124 (32.5)	258 (67.5)	<0.001
Placebo BID (N=382)	76 (19.9)	306 (80.1)	--

Abbreviations: BID = twice daily; BSS = Bristol Stool Scale; CMH = Cochran-Mantel-Haenszel; ITT = intent to treat

[a] *P* value is based on Chi-square test statistic

Pain Responders

Table 8 presents results from the CMH analysis of pain responders (individual pain component of the daily composite responder definition) over the intervals from Weeks 1-12 and Weeks 1-26. The proportion of pain responders for the 75-mg and 100-mg treatment groups was higher than placebo over the 3-month interval (Weeks 1-12) and the 6-month interval (Weeks 1-26); however, these differences were not statistically significant.

Table 8 CMH Analysis of Pain Responders (Daily Response Criterion; ITT Analysis Set)

Interval Treatment	Number (%)		*P* value[a]
	Responder	Non-Responder	
Weeks 1-12			
Eluxadoline 75 mg BID (N=381)	183 (48.0)	198 (52.0)	0.448
Eluxadoline 100 mg BID (N=382)	195 (51.0)	187 (49.0)	0.111
Placebo BID (N=382)	173 (45.3)	209 (54.7)	--
Weeks 1-26			
Eluxadoline 75 mg BID (N=381)	181 (47.5)	200 (52.5)	0.448
Eluxadoline 100 mg BID (N=382)	191 (50.0)	191 (50.0)	0.148
Placebo BID (N=382)	171 (44.8)	211 (55.2)	--

Abbreviations: BID = twice daily; CMH = Cochran-Mantel-Haenszel; ITT = intent to treat
[a] P value is based on Chi-square test

The proportion of pain responders in each of the 4-week intervals was higher than placebo for the 75-mg and 100-mg treatment groups; however, these differences were not statistically significant.

To further assess eluxadoline's effect on reducing patients' abdominal pain, Dr. Chen, the statistical reviewer, performed a mixed effects model for repeated measures (MMRM) analysis on patients' pain scores directly. Based on this exploratory analysis, both doses of eluxadoline appeared to show treatment benefit in treating patients' diarrhea and in reducing their abdominal pain. For detail analysis, please see Dr. Chen's full review dated on March 7, 2015.

Stool Consistency Responders
Table 9 presents results from the CMH analysis of stool consistency responders (individual stool consistency component of the daily composite responder definition) over the intervals from Weeks 1-12 and Weeks 1-26.

Table 9 CMH Analysis of Stool Consistency Responders (Daily Response Criterion)

Interval Treatment	Number (%)		*P* value[a]
	Responder	Non-Responder	
Weeks 1-12			
Eluxadoline 75 mg BID (N=381)	141 (37.0)	240 (63.0)	<0.001
Eluxadoline 100 mg BID (N=382)	136 (35.6)	246 (64.4)	<0.001
Placebo BID (N=382)	80 (20.9)	302 (79.1)	--
Weeks 1-26			
Eluxadoline 75 mg BID (N=381)	131 (34.4)	250 (65.6)	<0.001
Eluxadoline 100 mg BID (N=382)	152 (39.8)	230 (60.2)	<0.001
Placebo BID (N=382)	90 (23.6)	292 (76.4)	--

Abbreviations: BID = twice daily; BSS = Bristol Stool Scale; CMH = Cochran-Mantel-Haenszel; ITT = intent to treat
[a] P value is based on Chi-square test

The proportion of stool consistency responders for the 75-mg and 100-mg treatment groups was higher than that of placebo over the 3-month interval (Weeks 1-12) and the 6-month interval (Weeks 1-26).

The treatment group effect for stool consistency response was observed in each of the 4-week intervals for the 75-mg and 100-mg treatment groups with responder proportions being higher than that for placebo.Importantly, the population treatment group effects on stool consistency responders were demonstrated over the latter 2 intervals
(Weeks 17-20 and 21-24).

In conclusion, I concurred with Dr. Muldowney that data support efficacy in patients with IBS-D for both 75mg and 100mg. Previous registration trials in IBS-D (i.e., alosetron) assessed "adequate relief of IBS pain and discomfort". The currently designed analysis is more rigorous, but still shows similar improvement in symptoms over placebo.

For other efficacy endpoints assessments, please see Dr. Muldowney's full review.

8. Safety

Descriptive statistics were provided for safety endpoints. Summaries of adverse events were based on all events, regardless of study drug relationship, unless otherwise noted, and include summaries by intensity, adverse events that led to discontinuation, serious adverse events (SAEs), and treatment related SAEs. Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 11.0. All summarizations were performed using the preferred term by system organ class.

There have been a total of 2562 unique human exposures to oral eluxadoline during the clinical development program, including 2232 patients with IBS-d in the Phase 2 and 3 studies and 330 subjects in the Phase 1 oral administration studies. There have been a total of 520 and 541 patients exposed to 6 months of 75mg and 100mg BID treatment, respectively. In addition, there have been a total of 176 and 170 patients exposed to 12 months of treatment with eluxadoline 75mg and 100mg BID treatment, respectively.

Table 10: Duration of Exposure – Pooled Analysis Phase 2 and 3

	Eluxadoline 5 mg BID[a] (N=109)	Eluxadoline 25 mg BID (N=173)	Eluxadoline 75 mg BID (N=807[b])	Eluxadoline 100 mg BID (N=1032[b])	Eluxadoline 200 mg BID (N=171)	Placebo BID (N=975[b])	Total (N=3202)
Overall duration of exposure (days)							
n[c]	109	172	803	976	170	972	3202
Mean (SD)	65.5 (25.19)	72.8 (25.06)	211.9 (121.80)	186.0 (123.42)	63.6 (31.66)	190.9 (121.28)	177.3 (122.49)
Median	78.0	85.0	183.0	183.0	84.0	183.0	181.0
Min, Max	4, 97	1, 95	1, 384	1, 399	1, 103	1, 390	1, 399

Mean duration of exposure was similar between males and females within the 75-mg (219.7 and 207.9 days, respectively), 100-mg (192.4 and 182.9 days), and placebo (198.8 and 186.8 days) groups. The age inclusion criteria were 18 to 65 years (inclusive) for the Phase 2 study

and were 18 to 80 years (inclusive) for the two Phase 3 studies. Table 11 summarizes duration of exposure by age group (<65 years and ≥65 years) for the pooled Phase 2 and 3 studies using the Enrolled Set.

Mean duration of exposure was slightly shorter for patients who were under 65 years of age than for those who were ≥65 years of age for the 75-mg treatment group (210.8 and 224.4 days), 100-mg treatment group (185.3 and 195.0 days, respectively), and placebo group (187.2 and 222.6 days). It should be noted that only 243 patients who were ≥65 years of age received at least 1 dose of study drug in the Phase 2 and 3 studies, with nearly all exposures among patients ≥65 years of age occurring in the longer duration Phase 3 studies.

Table 11: Duration of Exposure by Age Group- Pooled Analysis Phase 2 and 3

Overall duration of exposure (days)	Eluxadoline 5 mg BID	Eluxadoline 25 mg BID	Eluxadoline 75 mg BID	Eluxadoline 100 mg BID	Eluxadoline 200 mg BID	Placebo BID	Total
Age group (years)							
<65							
n	107	171	740	902	170	869	2959
Mean (SD)	65.1 (25.31)	72.7 (25.12)	210.8 (122.08)	185.3 (122.87)	63.6 (31.66)	187.2 (120.98)	174.4 (122.00)
Median	78.0	85.0	183.0	183.0	84.0	183.0	180.0
Min, Max	4, 97	1, 95	1, 384	1, 399	1, 103	1, 390	1, 399
≥65							
n	2	1	63	74	0	103	243
Mean (SD)	82.5 (0.71)	85.0 (–)	224.4 (118.77)	195.0 (130.48)	0	222.6 (119.68)	212.9 (123.16)
Median	82.5	85.0	183.0	183.0	0	183.0	183.0
Min, Max	82, 83	85, 85	1, 372	2, 369	0	4, 378	1, 378

Mean duration of exposure was generally similar among patients who were White or Black within the 75-mg (213.6 and 203.0 days, respectively), 100-mg (187.2 and 189.2 days, respectively) and placebo groups (191.3 and 189.1 days, respectively). Only 359 Black patients and 89 patients who were categorized as “other” race received at least 1 dose of study drug in the Phase 2 and 3 studies. Among the 89 patients in the “other” race category, nearly one-third were enrolled in the shorter duration Phase 2 study.

The overall exposure to eluxadoline and duration of clinical trials during clinical development were adequate to assess the safety of the product.

Common Adverse Events

The overall incidence of AEs was comparable among all of the treatment groups, and in particular the proportions of patients with AEs were similar across the 75-mg (60.2%), 100-mg (55.7%), and placebo (54.7%) groups. Constipation occurred in a higher percentage of patients in the 75-mg (7.4%) and 100-mg (8.1%) eluxadoline treatment groups than in the placebo group (2.5%). A pooled summary of AEs that occurred in at least 2% of patients in any eluxadoline treatment group and at a greater incidence than placebo from the Phase 2 and 3 studies is provided in Table 12.

Table 12: Adverse Events Reported by ≥2% of Patients in any Eluxadoline Treatment Group and at a Greater Incidence than Placebo - Pooled Phase 2 and 3 Studies

System Organ Class Preferred Term	Number (%) of Patients Eluxadoline 5 mg BID (N=109)	Eluxadoline 25 mg BID (N=173)	Eluxadoline 75 mg BID (N=807)	Eluxadoline 100 mg BID (N=1032)	Eluxadoline 200 mg BID (N=171)	Placebo BID (N=975)
Total number of AEs	100	224	1556	1804	238	1573
Number of patients with ≥1 AE	48 (44.0)	86 (49.7)	486 (60.2)	575 (55.7)	91 (53.2)	533 (54.7)
Gastrointestinal disorders	**20 (18.3)**	**38 (22.0)**	**242 (30.0)**	**273 (26.5)**	**48 (28.1)**	**185 (19.0)**
Nausea	6 (5.5)	10 (5.8)	65 (8.1)	73 (7.1)	18 (10.5)	49 (5.0)
Constipation	2 (1.8)	5 (2.9)	60 (7.4)	84 (8.1)	6 (3.5)	24 (2.5)
Abdominal pain	3 (2.8)	6 (3.5)	33 (4.1)	47 (4.6)	13 (7.6)	25 (2.6)
Vomiting	1 (0.9)	7 (4.0)	32 (4.0)	43 (4.2)	12 (7.0)	12 (1.2)
Flatulence	1 (0.9)	3 (1.7)	21 (2.6)	33 (3.2)	4 (2.3)	17 (1.7)
Abdominal distension	0	0	21 (2.6)	28 (2.7)	1 (0.6)	15 (1.5)
Dry mouth	1 (0.9)	4 (2.3)	15 (1.9)	13 (1.3)	5 (2.9)	15 (1.5)
Diarrhea	0	8 (4.6)	14 (1.7)	13 (1.3)	2 (1.2)	10 (1.0)
Gastroesophageal reflux disease	2 (1.8)	5 (2.9)	11 (1.4)	13 (1.3)	1 (0.6)	10 (1.0)
Infections and infestations	**18 (16.5)**	**30 (17.3)**	**199 (24.7)**	**222 (21.5)**	**25 (14.6)**	**230 (23.6)**
Upper respiratory tract infection	3 (2.8)	5 (2.9)	27 (3.3)	53 (5.1)	1 (0.6)	38 (3.9)
Nasopharyngitis	5 (4.6)	8 (4.6)	33 (4.1)	31 (3.0)	6 (3.5)	33 (3.4)
Sinusitis	5 (4.6)	6 (3.5)	27 (3.3)	27 (2.6)	1 (0.6)	35 (3.6)
Bronchitis	4 (3.7)	4 (2.3)	26 (3.2)	30 (2.9)	1 (0.6)	21 (2.2)
Gastroenteritis viral	1 (0.9)	3 (1.7)	22 (2.7)	14 (1.4)	4 (2.3)	18 (1.8)
Urinary tract infection	0	2 (1.2)	17 (2.1)	18 (1.7)	4 (2.3)	17 (1.7)
Nervous system disorders	**8 (7.3)**	**17 (9.8)**	**81 (10.0)**	**112 (10.9)**	**24 (14.0)**	**99 (10.2)**
Headache	3 (2.8)	12 (6.9)	32 (4.0)	44 (4.3)	7 (4.1)	44 (4.5)
Dizziness	4 (3.7)	4 (2.3)	21 (2.6)	33 (3.2)	11 (6.4)	21 (2.2)
Somnolence	1 (0.9)	1 (0.6)	1 (0.1)	11 (1.1)	4 (2.3)	3 (0.3)

System Organ Class Preferred Term	Number (%) of Patients Eluxadoline 5 mg BID (N=109)	Eluxadoline 25 mg BID (N=173)	Eluxadoline 75 mg BID (N=807)	Eluxadoline 100 mg BID (N=1032)	Eluxadoline 200 mg BID (N=171)	Placebo BID (N=975)
Investigations	**5 (4.6)**	**8 (4.6)**	**77 (9.5)**	**70 (6.8)**	**4 (2.3)**	**78 (8.0)**
Alanine aminotransferase increased	2 (1.8)	0	17 (2.1)	26 (2.5)	1 (0.6)	14 (1.4)
General disorders and administration site conditions	**5 (4.6)**	**9 (5.2)**	**47 (5.8)**	**64 (6.2)**	**15 (8.8)**	**65 (6.7)**
Fatigue	2 (1.8)	3 (1.7)	21 (2.6)	20 (1.9)	4 (2.3)	23 (2.4)
Respiratory, thoracic, and mediastinal disorders	**4 (3.7)**	**10 (5.8)**	**58 (7.2)**	**55 (5.3)**	**7 (4.1)**	**66 (6.8)**
Cough	0	5 (2.9)	13 (1.6)	9 (0.9)	1 (0.6)	19 (1.9)
Vascular disorders	**0**	**4 (2.3)**	**25 (3.1)**	**25 (2.4)**	**7 (4.1)**	**25 (2.6)**
Hypertension	0	3 (1.7)	20 (2.5)	14 (1.4)	5 (2.9)	16 (1.6)

Abbreviations: AE = adverse event; BID = twice daily; SOC = system organ class

Notes: For the SOC and preferred term level summaries, multiple occurrences of an SOC or preferred term within a patient are counted once only. All occurrences of a preferred term are included in the total number of AEs. All AEs with a start date between treatment start date and date of last study visit inclusive (or last contact date if last study visit was missing) are included.

Source: ISS Amendment Table 2.29

Deaths

No patient died while participating in any study during the eluxadoline clinical development program. In Phase 3 Study IBS-3001, 1 patient (Patient 138/0001) died (b) (6) days after receiving the last dose of study drug, and following an SAE of lower extremity cellulitis.

Patient 138/0001 from IBS-3001 was a 51-year-old female patient who died (b) (6) days after receiving her last dose of eluxadoline. In total, she received eluxadoline for (b) (6)

days, (b) (6). She was randomized to 75mg BID which she received for 127 days. Due to an IVRS error, she then received 100mg BID for 31 days. (b) (6) after receiving her last dose of study drug, the patient was hospitalized for left lower leg cellulitis ((b) (6)). On 28February2013, she returned to the study site for study termination procedures and was noted to have left lower leg redness secondary to cellulitis. Her physical exam, vital signs, and ECG were otherwise unchanged from her baseline examination. Laboratory testing was unremarkable. (b) (6) days after her study termination visit ((b) (6) days after last dose of study drug), she was found dead at home.

The patient's medical history and concurrent conditions included cardiac catheterization, type 2 diabetes mellitus, morbid obesity (BMI of 49 kg/m^2), asthma, hypertension, hyperlipidemia, sleep apnea syndrome, gastroesophageal reflux disease, hypothyroidism, nephrolithiasis, insomnia, depression, suicide attempt, back pain, rhinitis, migraine, eczema, anxiety, osteoarthritis, rosacea, vitamin D deficiency, and hypersensitivity. At the time of death, concomitant medications included alprazolam, zolpidem tartrate, amitriptyline, atenolol, eclecoxib, methylcellulose, valproate, semisodium, levothyroxine, hydrocortisone butyrate cream, omeprazole, methocarbamol, sumatriptan, paracetamol, salbutamol sulfate, liraglutide, vilazodone, colecalciferol, cetirizine hydrochloride, atorvastatin, ceftriaxone, clotrimazole, furosemide, lactobacillus acidophilus, metronidazole, miconazole, mupirocin, potassium citrate, triamcinolone, and heparin. The death was labeled as arteriosclerotic cardiovascular disease, and the investigator assessed both the cellulitis and arteriosclerosis coronary artery as not related to study drug.

I agree with Dr. Muldowney and the investigator's assessment that this death was unlikely related to study drug, rather was likely related to the patients comorbidities. Adverse events, including SAEs and deaths, should continue to be routinely collected and assessed in the postmarketing setting.

Serious Adverse Events

The proportions of patients with SAEs were the 75-mg (4.2%), 100-mg (4.0%), and placebo (2.6%) groups. SAEs were most often reported within the GI disorders (0.9% of all patients) that occurred in similar proportions of patients in the 75-mg and 100-mg treatment groups (1.0% and 1.3%, respectively), compared with 0.4% of placebo patients.

The SAE with the overall highest incidence while taking eluxadoline was pancreatitis (this includes the terms "pancreatitis," "acute pancreatitis," and "alcoholic pancreatitis"). A total of 11 cases of pancreatitis were reported. Nine of the eleven were independently adjudicated as pancreatitis.

Similar proportions of patients in the 75-mg and 100-mg eluxadoline groups experienced SAEs of acute pancreatitis (2/807, 0.2% and 3/1032, 0.3%, respectively) and pancreatitis (0.1% each group). One (0.6%) patient in the 200-mg group experienced an SAE of alcoholic pancreatitis. A detailed discussion of pancreatitis events is provided in Section of Special Interesting Adverse Events in this review.

In addition, 2 patients in Study IBS-3001 had an SAE of small bowel obstruction, 1 patient from the placebo arm and 1 patient from the 100mg arm. One patient in IBS-3002 in the 100mg treatment arm had an SAE of ischemic colitis, and another patient had an SAE of suicide attempt. Finally, 2 patient had SAE of spontaneous abortion. These serious events are briefly described below.

- Patient IBS-3001 255/0003 in the placebo group had an SAE of small bowel obstruction.

- Patient 083/0012 with a history of a tubal ligation 30 years prior to randomization in the 100-mg treatment group was hospitalized due to an SAE of small bowel obstruction secondary to ileal stricture. In the first 6 months her diary demonstrates only a single day of no bowel movement and she experienced no AEs of constipation nor diary confirmed constipation. This patient was on treatment for (b) (6) days before she was admitted to the hospital. Upon admission, she had had no bowel movement or passage of flatus for 2 days. A CT scan revealed small bowel obstruction with transition point within the right mid pelvis just to the right of midline, mild abdominal ascites, bowel wall thickening, and diverticulosis. On the day after admission, the patient had an exploratory laparotomy demonstrating the ileal stricture and subsequently underwent two small bowel resections. I agreed this case of small bowel obstruction is not study drug related.

- Patient IBS-3002 800/0004, a 72-year old female patient with IBS-D and multiple comorbid conditions including hepatic cirrhosis, thrombocytopenia, sinus bradycardia, diverticulum, hemorrhoids, type II DM, COPD, hypertension, hyperlipidemia, secondary hyperparathyroidism, GERD, osteoarthritis, depression, anxiety, chronic renal failure, iron deficiency anemia, and recent Escherichia sepsis and pseudomonal sepsis (2.5 months prior to randomization). Concomitant medications at the time of randomization in IBS-3002 included acetylsalicylic acid, gabapentin, lovastatin, omeprazole, psyllium hydrophilic mucilloid, sertraline, temazepam, and Ursodeoxycholic acid. The patient began eluxadoline 100mg twice daily on (b) (6). On (b) (6) days after her first dose of eluxadoline, the patient developed abdominal pain, nausea, and vomiting, followed by rectal bleeding and hypotension (reported as 80/40 prior to arrival in the ED). She was admitted to the hospital with ischemic colitis. At the time of admission, her PT, PTT, and INR were slightly prolonged (13.6 seconds, 31.4 seconds, and 1.08, respectively). Colonoscopy showed patchy areas of ischemic appearing colitis, and no active source of bleeding was identified. She was treated with IV fluids, metronidazole, levofloxacin, loperamide, macrogol, magnesium citrate, pantoprazole, and ondansetron, and eluxadoline was permanently discontinued. She was discharged from the hospital on (b) (6) and recovered with no sequelae. The investigator reported the AE as unlikely related to study drug. The Applicant assessed this event as unlikely related to study drug. They assessed the patient at high risk for gastrointestinal bleeding due to multiple comorbidities which may have contributed to the event, particularly hepatic cirrhosis, thrombocytopenia, coagulopathy, renal failure, h/o diverticulosis and internal

hemorrhoids, and prophylactic aspirin use. By history, the patient's bleeding was associated with a drop in BP prior to arrival in the hospital which may have precipitated the ischemic event. Finally, diary data from the patient in the days prior to the event show no evidence of constipation, in fact, the patient was reporting 2-3 bowel movements per day (BSS 6), consistent with diarrhea, which demonstrated the lack of efficacy and continued diarrhea prior to the onset of symptoms of ischemic colitis. I concur with this assessment.

- One patient (0.1%) in the 100-mg group had an SAE of suicide attempt. Patient IBS-3002 672/0021 with a prior history of depression for which no concomitant medications were taken, had an SAE of suicide attempt on Day (b) (6) when she took 6 Tylenol PM pills. The patient reported that she was having difficult times involving her ex-husband that caused her to have an extremely high stress level and resulted in her suicide attempt. A nonserious adverse event of bipolar affective disorder was also reported during this time. Study drug was temporarily stopped due to the suicide attempt.

- One SAE of spontaneous abortion was reported (IBS-3001 268/0018) in the 75-mg group. The patient was withdrawn from the study due to the pregnancy and the outcome of the pregnancy was followed. This patient was physically abused by her boyfriend (rib fractures) and had a spontaneous abortion. One additional patient in the 100-mg group (IBS-3001 309/0032) who was discontinued from the study due to pregnancy experienced a spontaneous miscarriage after her exit from the study (this subject had a history of 2 prior miscarriages).

Adverse Events Leading to Withdrawal or Treatment Interruption

The proportions of patients discontinued due to an AE were comparable between the 75-mg and 100-mg treatment groups (8.3% and 7.8%, respectively), compared with 4.3% of placebo patients. The highest rate of patients discontinued due to an AE (12.9%) was in the 200-mg eluxadoline group.

Adverse events resulting in discontinuation were most often reported within the GI disorders, and occurred with greater frequency in the 200-mg eluxadoline treatment group (10.5%) than at lower doses or with placebo. Similar proportions of patients in the 75-mg and 100-mg groups had GI events that led to discontinuation (4.7% and 4.9%, respectively), compared with 1.7% of placebo patients.

The AEs that most commonly led to discontinuation for patients who received eluxadoline were abdominal pain and constipation; and all other AEs in either the 75- or 100-mg dosing groups resulting in discontinuation were reported for ≤0.6% of patients. Similar proportions of patients across the 75-mg, 100-mg, and placebo groups were discontinued due to AEs of abdominal pain (1.1%, 1.1%, and 0.3%, respectively) and constipation (1.1%, 1.5%, and 0.3%, respectively).

Table 13: Adverse Events Leading to Treatment Discontinuation for ≥1% of Patients in any Treatment Group – Pooled Phase 2 and 3 Studies

	Number (%) of Patients					
Preferred Term	Eluxadoline 5 mg BID (N=109)	Eluxadoline 25 mg BID (N=173)	Eluxadoline 75 mg BID (N=807)	Eluxadoline 100 mg BID (N=1032)	Eluxadoline 200 mg BID (N=171)	Placebo BID (N=975)
Adverse events	3	7	68	84	48	46
Number of patients with ≥1 AE leading to discontinuation	2 (1.8)	5 (2.9)	67 (8.3)	80 (7.8)	22 (12.9)	42 (4.3)
Abdominal pain	0	1 (0.6)	9 (1.1)	11 (1.1)	10 (5.8)	3 (0.3)
Constipation	0	0	9 (1.1)	15 (1.5)	4 (2.3)	3 (0.3)
Nausea	0	1 (0.6)	5 (0.6)	0	4 (2.3)	4 (0.4)
Abdominal pain upper	0	0	3 (0.4)	4 (0.4)	2 (1.2)	0
Headache	0	0	3 (0.4)	1 (0.1)	3 (1.8)	1 (0.1)
Dizziness	0	0	1 (0.1)	1 (0.1)	3 (1.8)	2 (0.2)
Vomiting	0	0	1 (0.1)	2 (0.2)	2 (1.2)	1 (0.1)
Fatigue	0	0	0	0	2 (1.2)	2 (0.2)
Dry mouth	0	0	0	0	3 (1.8)	0
Somnolence	0	0	0	1 (0.1)	2 (1.2)	0
Pruritus	0	0	1 (0.1)	0	2 (1.2)	0

Abbreviations: AE = adverse event; BID = twice daily; SOC = system organ class

Notes: For the SOC and preferred term level summaries, multiple occurrences of an SOC or preferred term within a patient are counted once only. All occurrences of a preferred term are included in the total number of AEs. All AEs with a start date between treatment start date and date of last study visit inclusive (or last contact date if last study visit was missing) are included.

Source: ISS Amendment Table 2.49

Overall, discontinuations due to AEs commonly occurred early in the course of treatment (ie, within the first 2 weeks). Of the 218 patients who discontinued due to AEs, 48.2% (105 of 218) discontinued within the first 2 weeks of dosing. Similar proportions of patients in the 75-mg and 100-mg groups (3.3% and 3.7%, respectively) were discontinued during this time compared with 1.6% of placebo patients and 11.7% of patients in the 200-mg group.

Among the 40 cases of abdominal pain that led to discontinuation after starting study drug (including event terms of "abdominal pain," "abdominal distension," "dyspepsia," and "abdominal discomfort"), 19 occurred within 1 calendar day of study drug initiation (IBS-2001 Patients 008/0009, 043/0002, 050/0028, 092/0005, 128/0003, 193/0004, and 242/0007; IBS-3001 Patients 107/0001, 126/0002, 148/0005, and 257/0001; and IBS-3002 Patients 591/0003, 641/0008, 654/0017, 700/0028, 753/0003, 812/0002, 557/0013, and 611/0004). Laboratory testing to check for elevation of liver or pancreatic enzymes for those events of abdominal pain was either not done (the vast majority) or, if done, yielded results that were normal. Importantly, in Phase 3, 7 of the 12 patients who experienced these events had prior cholecystectomies (cholecystectomy status was not prospectively captured in Phase 2). The clinical presentation and the prevalence of prior cholecystectomy are similar to those events that are described as spasm of the sphincter of Oddi. However, without appropriate supportive laboratory data, these events could have alternative etiologies including background abdominal pain.

Similar proportions of patients in the 75-mg and 100-mg eluxadoline groups were discontinued as the result of a GI disorders AE within the first 12 weeks (4.0% and 4.5%) and 26 weeks (4.6% and 4.7%) of treatment. In comparison, 1.7% of placebo patients were discontinued due to a GI AE during these times.

Special Interesting Adverse Events

Constipation Events
The overall incidence of constipation AEs was higher in the 75-mg (7.4%) and 100-mg (8.1%) groups, compared with 2.5% of placebo patients. Of the patients in the 75-mg and 100-mg groups who ever reported AEs of constipation, approximately 80% reported constipation AEs within the first quarter; these data indicate that if patients experienced constipation it was most likely to occur within the first 13 weeks of treatment.

Constipation events are potential adverse events for this drug. Patients should be contraindicated if patients with 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.

Adverse Events Consistent with Sphincter of Oddi Spasm
Furiex established a safety-focused adjudication committee outside of the protocols to evaluate whether blinded adverse events in IBS-3001 and IBS-3002 met prespecified case definitions for pancreatitis and acute hepatobiliary events, and to determine the potential etiology of sphincter oddi spasm in these events. For an event to be adjudicated, it had to be a suspected pancreatitis or hepatobiliary event. Adverse events listings for both IBS-3001 and IBS-3002 were reviewed on a weekly basis and suspected hepatobiliary and suspected pancreatitis cases were identified based on the coded AE terms.

The committee also adjudicated 4 unblinded suspected cases of pancreatitis and 1 suspected acute hepatobiliary event from the completed Phase 2 study (IBS-2001).

Pancreatitis was defined based on the standardized criteria as described by Banks and colleagues in “Classification of Acute Pancreatitis-2012: Revision of the Atlanta classification and Definitions by International Consensus”. For all cases of pancreatitis, the committee’s pancreatitis and sphincter of Oddi expert, Dr. Peter Cotton, was asked to provide an assessment of severity based on the Atlanta criteria; and an overall clinical assessment of the case. Table 14 provides a summary of patients with adjudicated pancreatitis events in the developmental program for eluxadoline.

Table 14 Summary of Pancreatitis Cases – Pooled Phase 2 and 3 Studies

Total Pancreatitis Cases in ISS Database[a]	11
Cases Adjudicated as Pancreatitis[b]	9
Cases on Eluxadoline at Time of Onset of Pancreatitis[a]	8
Cases Adjudicated as Consistent with SO Spasm	3
Cases Associated with EtOH	4
Cases Associated with Biliary Sludge	1

Abbreviations: EtOH = alcohol; ISS = Integrated Summary of Safety; SO = sphincter of Oddi

Notes: Table presents data across all eluxadoline dose levels evaluated in the Phase 2 and 3 studies (ie, not limited to 75 mg and 100 mg).

[a] One pancreatitis event occurred after the patient's withdrawal from Study IBS-2001 and is not depicted in ISS Amendment Table 2.29, but is captured within the ISS database.

[b] As adjudicated by the Hepatobiliary and Pancreatitis Adjudication Committee based on Atlanta Criteria for pancreatitis. Two patients, IBS-3001 112/0006 and IBS-3001 145/0004 failed to meet Atlanta Criteria for the diagnosis of pancreatitis.

An acute hepatobiliary event was defined as consisting of ALL of the following 3 criteria:
1. Abdominal pain suggestive of biliary origin (epigastric or right upper quadrant pain), with the start of such pain considered to be the onset of the acute hepatobiliary event;
2. Serum ALT or AST levels 3 or more times normal, or 2 times an elevated baseline value (if that value is >3xULN); and
3. Event prompted study drug withdrawal.

There were a total of 9 cases adjudicated as Acute Hepatobiliary Events and all of 9 cases were consistent with sphincter of Oddi (SO) Spasm. Among them, 8 of 9 cases were with absent gall bladder and 1 case with unknown gall bladder anatomy.

There were 3 cases of SO spasm associated with events meeting the definition for pancreatitis All 3 patients had a prior cholecystectomy and had study drug discontinued at the onset of these events. All cases were transient and occurred during the first day of treatment. All patients were briefly hospitalized with no complications. The severity of all cases was rated as mild, based on the Atlanta criteria (*Gut*2013;62:102-111 Classification of acute pancreatitis). Alcohol was an alternative etiology in one case adjudicated as SO spasm (IBS-2001 277/0001) because the patient had recent alcoholic pancreatitis and presented with an elevated blood alcohol level. For each case listed in Table 15.

Table 15 Pancreatitis Events Adjudicated as SO Spasm

Patient	Dose (mg)	Age/Gender	Severity (Atlanta Criteria)	Peak lipase (Value/ULNx[a])	Prior Cholecystectomy (Yes/No)	EtOH (Yes/No)	Sponsor Comments
IBS-2001 074/0001	200	29/F	mild	14,825/49x[b]	Yes	No	29-year-old obese diabetic female s/p cholecystectomy presented with abdominal pain, nausea, and vomiting with increased pancreatic enzymes several hours after first dose, which then declined rapidly. Lipase was within normal limits ~2 days; case likely represents eluxadoline-related SO spasm. **Dr. Peter Cotton's Assessment:** Probably drug related. No other cause evident, started immediately after commencement and settled quickly after discontinuation.
IBS-2001 277/0001	200	51/F	mild	7549/19.2x[c]	Yes	Yes	51-year-old female smoker, s/p cholecystectomy, with recent alcoholic pancreatitis prior to study, was instructed to avoid alcohol. Presented to emergency room with pain, increased lipase after 2 doses of study drug, with elevated blood alcohol and recurrence of pancreatitis. Study site reported the event as "alcoholic pancreatitis." **Dr. Peter Cotton's Assessment:** Pancreatitis probably mainly due to alcohol (prior episode alcoholic pancreatitis documented 3 months prior to study), but the drug could possibly have contributed through sphincter dysfunction, since she is post-cholecystectomy.
IBS-3001 144/0003	100	62/F	mild	3318/8.44x[d]	Yes	No	62-year-old female s/p cholecystectomy experienced mild transient pancreatitis with normal pancreas on CT. Symptoms occurred in minutes after first dose and lipase returned to nearly normal in 24 hours. Likely drug-related sphincter of Oddi spasm. **Dr. Peter Cotton's Assessment:** Probably drug related. No other etiology apparent, prior cholecystectomy and pancreatitis occurred very soon after treatment initiation.

Abbreviations: CT = computed tomography; EtOH = alcohol; SO = sphincter of Oddi; s/p = status post; ULN = upper limit of normal

[a] Value presented represents the magnitude relative to the upper limit of normal (ULN). The ULN for all pancreatitis cases is based on reference ranges for the local hospitals or emergency rooms where patients were evaluated.

[b] Value had decreased to 1,582 (5.3xULN) approximately 30 hours later.

[c] Value had decreased to 1436 (3.6xULN) approximately 10.5 hours later.

[d] Value had decreased to 1909 (4.8xULN) approximately 16.5 hours later.

Sources: HPAC Summary of Findings Table 4-2, Module 5.3.5.3; Patient narratives appended to CSR IBS-2001, CSR IBS-3001, and CSR IBS-3002.

One additional event adjudicated by the HPAC committee as SO spasm of the pancreas did not meet the Atlanta Criteria for pancreatitis. Of note, this patient also had a prior cholecystectomy.

Patient 112/0006 from **Study** IBS-3001 **w**as a 65-year-old female s/p cholecystectomy presented with nausea and abdominal pain after 2 doses of 75mg study drug. Lipase peak was 1.6xULN and normalized within 24 hours of stopping treatment. Normal pancreas was on CT scan. Adverse event was reported by the study site as "mild pancreatitis".

Pancreatitis, acute hepatobiliary events and acute hepatobiliary spasm or sphincter of Oddi spasm are potential adverse events for this drug. These patients are at increased risk for those events should be contraindicated that include patients with a history of pancreatitis; or structural diseases of the pancreas; known or suspected pancreatic duct obstruction, known or suspected biliary duct obstruction; or sphincter of Oddi disease or dysfunction.

Cardiac and Chest Pain Events

Cardiac disorders AEs were reported 1.5%, 1.8%, and 1.1% respectively in patients across the 75-mg, 100-mg, and placebo groups.

No patient treated with 5 mg eluxadoline experienced a cardiac-related AE. Angina pectoris was reported in 0.5% (4/807), 0.4% (4/1032), and 0.1% (1/975) of patients in the 75-mg, 100-mg, and placebo groups, respectively. Palpitations were reported in 0.1% (1/807), 0.4% (4/1032), and 0.2% (2/975) of patients in the 75-mg, 100-mg, and placebo groups, respectively.

Among the Phase 3 patients treated with 75 mg or 100 mg eluxadoline, 11 patients experienced serious events typical of acute coronary syndrome; 4/11 patients reported only chest pain events. Additionally, Patient IBS-3001 138/0001 (75-mg treatment group) experienced an SAE of coronary artery arteriosclerosis that resulted in sudden death (found at home) after the patient had discontinued from the study, and (b) (6) days after the last dose of study medication that is unlikely related to study drug.

Overall, pertinent cardiac events occurring on eluxadoline were either a clear exacerbation of background illness, likely related to other medications, strongly suspicious for alternative etiology, or suggestive of SO spasm. Of 31 patients treated with 75-mg or 100-mg eluxadoline in the Phase 3 studies who experienced events typical of acute coronary syndrome, 18 patients had a prior cholecystectomy and 8 patients were ≥65 years of age.

Table 16 Analysis of Major Adverse Cardiovascular Events (MACE)

Patient Number	Event Details
75 mg Eluxadoline	
IBS-3001 138/0001	Sudden death (patient found at home) (b) (6) weeks after stopping study drug
IBS-3001 124/0014	Acute MI
100 mg Eluxadoline	
IBS-3001 016/0009	Acute asthma with acute stress MI possibly secondary to beta agonists
IBS-3001 191/0002	Coronary stent required 3 separate times during 1 year study; troponin negative
IBS-1005 501/0001	Acute MI in subject with hepatic failure (b) (6) days after single dose of eluxadoline; required a stent. Systemic eluxadoline was below limit of quantification at 96 hours post-dose
Placebo	
IBS-3001 064/0012	Acute hemiparesis possibly secondary to hypertension
IBS-3002 613/0007	Troponin negative. Stent required.
IBS-3002 781/0004	Elective CABG required

Abbreviations: MI = myocardial infarction; CABG = coronary artery bypass grafting

In this NDA, MACE was defined by the sponsor as non-fatal MI, non-fatal stroke, cardiovascular death, or requirement for a major cardiac procedure (CABG or coronary stent placement). Suspected events were not adjudicated as listed in the table above. Including CABG, stent or TIA in MACE analysis can add enough noise to remove a signal. Therefore, the FDA position is to not include those. Based on FDA position, there were 2 MACE events in the 75 mg arm (IBS-3001 138/0001 and IBS-3001 124/0014), 2 events in the 100 mg arm

(IBS-3001 016/0009 and IBS-1005 501/0001) and no events in the placebo arm. More detail information regarding those 4 cases are provided in the section below.

Two cases IBS-1005 501/0001 and IBS-3001 138/0001 were confounded by extreme latency periods as the events occurred at a distant point in time after the patient had stopped taking eluxadoline. Patient IBS-1005 501/0001, a subject with moderate hepatic impairment, experienced an acute myocardial infarction (b) (6) days after a single 100-mg oral dose of eluxadoline; systemic levels were below the limit of quantification at 96 hours postdose. This patient had hepatic impairment at baseline and his hepatic impairment was not related to study drug. Patient IBS-3001 138/0001 experienced sudden death (b) (4), (b) weeks after stopping BID treatment with 75 mg eluxadoline. This case was confounded by the patient's medical history which included diagnoses associated with sudden death, ie, type 2 diabetes mellitus, morbid obesity, hypertension, hyperlipidemia, sleep apnea syndrome, beta agonist-treated chronic asthma, and a temporally related hospitalization for lower extremity cellulitis.

Less than 2% of an orally administered dose of eluxadoline is detected in the systemic circulation while >80% is recovered in the feces in ≤2 weeks. What little drug is available systemically demonstrates a time to maximum concentration of 1 to 2 hours and a mean apparent alpha half-life during the distribution phase of approximately 2 to 4 hours. No drug is detected in systemic circulation after 48 hours at doses below 300 mg.

Given the elapsed time since the last dose of blinded study drug, I believed that eluxadoline was not contributed as a cause of these major adverse cardiovascular events.

Two remaining events (IBS-3001 016/0009 and IBS-3001 124/0014) involved myocardial infarctions. IBS-3001 016/0009, a 71-year-old female, after her first dose of 100 mg eluxadoline, was hospitalized (b) (6) days for acute exacerbation of bronchial asthma which was associated with increasing use of beta agonists; ultimately acute respiratory failure ensued. Additionally, she experienced a non-ST myocardial infarction with positive cardiac enzymes. However, due to normal coronary arteries and apical dyskinesia, the patient was subsequently diagnosed with Takotsubo syndrome (stress cardiomyopathy). IBS-3001 124/0014 involved a 79-year-old male with medical history of cerebrovascular accident (2007 and 2008), myocardial infarction (2008), coronary artery stent placement (2008 and 2010), coronary artery bypass graft (five vessel) (2011), hypertension, hypercholesterolemia, peripheral vascular disease, and diabetes mellitus. He experienced an acute myocardial infarction (b) (6) days after the first dose of study drug and was found to have an occluded left main coronary artery. He was successfully treated with placement of a drug eluting stent and had a full recovery without sequelae.

Given the medical history of these patients, including the known risk factors for cardiac events, and concomitant medications, I believed that there is no reasonable possibility that eluxadoline contributed as a cause of these major adverse cardiovascular events.

The primary concern with opioid receptor antagonists in the recent past was with mu opioid receptor antagonists (Relistor, Movantik). Movantik was approved with a PMR – an

observational study comparing Movantik with other opioid induced constipation treatments with a primary outcome of MACE.

Eluxadoline is primarily locally acting and has extremely low oral bioavailability, so there would be minimal ability to affect the systemic/cardiac delta opioid receptors. There was no evidence of cardiovascular AE, impact on vitals, or ECG changes in the eluxadoline Phase 2/3 studies. Phase 3 trial was conducted with 52-week double-blind safety assessments. There was some orthostatic hypotension observed at supra-therapeutic doses (500mg) in FIH studies, so the Applicant used holter monitoring and closely monitored BPs during Phase 2, but there was no evidence of an impact on BP. Therefore, I concurred with Dr. Muldowney that no specific CV postmarketing monitoring/studies are currently needed for eluxadoline. It doesn't appear there is a strong evidence that eluxadoline would increase the risk for cardiovascular events.

The sponsor conducted a Thorough QT Study that was reviewed by FDA Thorough QT Review Team. The team concluded that no significant QTc prolongation effect of JNJ-27018966 (100 mg and 1000 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between JNJ-27018966 100 mg and placebo, and between JNJ-27018966 1000 mg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms, indicating that assay sensitivity was established.

The supratherapeutic dose (1000 mg) produced mean Cmax values 10-fold the mean Cmax for the therapeutic dose (100 mg). These concentrations are above those for the predicted worst case clinical scenario (drug interaction with cyclosporine). The results show that at these concentrations there are no detectable prolongations of the QT-interval. The only cardiovascular adverse event was palpitations in one subject on the high dose. Overall ECG acquisition and interpretation in this study appears acceptable. There was no clinically relevant effect on PR or QRS.

Drug Abuse

Abuse potential studies were completed using oral and intranasal eluxadoline. Intravenous abuse potential studies were felt to be unethical due to safety concerns; however, the Applicant completed a study self-injection study in Rhesus monkeys. Monkeys discriminated injected eluxadoline as a Mu opioid and worked for continued injections. In the oral and intranasal abuse studies in humans, euphoric mood and somnolence were reported at higher rates in eluxadoline treated patients than placebo, though these rates were significantly lower than rates observed with oxycodone.

(b) (4)

I concurred with Dr. Muldowney and agree with this conclusion. However, there was an increase in AEs of euphoric mood compared to placebo. There was also an increase in AEs of somnolence in the eluxadoline 100mg and 300mg treatment groups (31.4% 100mg, 41.7% 300mg) compared to placebo (18.9%), however, the percentage of patients with an AE of somnolence from the 1000mg group was 19.4%, making interpretation difficult. While

intranasal eluxadoline was associated with higher euphoric mood than placebo, the percentages were significantly lower than with oxycodone IR, and the Applicant suggests these AEs were commonly associated with nasal congestion, sore throat, dysgeusia, and significant disliking, making abuse unlikely.

There was no increase in AEs of abuse, withdrawal, or rebound in during clinical studies in IBS-D patients, suggesting there should be no significant impact on patients using eluxadoline as indicated.

Eluxadoline does cross the blood brain barrier. The key concern of the CSS staff is whether opioid abusers, given access to injectable eluxadoline, would persistently inject it. No injections studies were completed in humans, as this was not felt to be safe; however, a study was completed in Rhesus monkeys. Monkeys discriminate injected eluxadoline as a Mu opioid and work for continued injections of it. Based on the primate data, CSS believes opioid abusers would persistently inject an IV formulation of eluxadoline. CSS believes the true test of abuse potential will come with the social experiment occurring over the first year of the drug's public availability: "How many reports will be found of illicit drug users (and/or their suppliers) diverting, synthesizing, or otherwise obtaining and repeatedly injecting eluxadoline in some form?"

At the time of this review, the Controlled Substance Staff (CSS) of FDA recommend a scheduling III. We had a meeting with the sponsor and the sponsor agreed with scheduling IV, (b) (4). The sponsor did provide more data for FDA CSS review and such review is ongoing now. A final decision on scheduling will be made after reviewing the additional data. Please see the CSS primary review by Dr. Alan Trachtenberg.

Overall Safety Conclusions
A total 1001 patients have been exposed to 6 months of treatment with eluxadoline while 488 patients have been exposed to 12 months of treatment with eluxadoline. Eluxadoline is tolerated with the most common nonserious AEs (<10%) of nausea, constipation, and abdominal pain seen in IBS-d patients. The AEs that most commonly led to discontinuation were abdominal pain and constipation. The proportions of patients across the 75-mg, 100-mg, and placebo groups who discontinued were: abdominal pain (1.1%, 1.1%, and 0.3%, respectively) and constipation (1.1%, 1.5%, and 0.3%, respectively).

Pancreatitis events consistent with known opiate effects seen in the pooled Phase 2 and 3 studies (0.35%) were mild, short-lived with no sequelae, and all associated either with biliary disorders (SO spasm and biliary sludge) or alcohol use. Similarly, hepatobiliary events consistent with SO spasm seen in the pooled Phase 2 and 3 studies (also 0.35%) presented with acute symptoms prompting discontinuation of medication, resolved rapidly, had no sequelae, and were highly correlated with the absence of a gall bladder.

Please refer to Dr. Muldowney's complete review.

9. Advisory Committee Meeting

NA

10. Pediatrics

This drug has not yet been studied in children. The applicant has requested a Waiver of Pediatric Study for pediatric patients from birth to <6 years of age. I agree that conduct of studies in this age group is impracticable due to the low prevalence of the disorder. The sponsor also requested a Deferral of Pediatric Study for pediatric patients ≥ 6 to 17 years and 11 months. I concur. We generally have waived requirements for pediatric studies of IBS-C treatments in children under the age of 6 due to the low IBS incidence in that age group. We presented the plan to the FDA Pediatric Research Committee (PeRC) and PeRC concurred with the plan.

At the time of this review, the Applicant agreed to the following pediatric (PMR) studies under PREA:

- A Randomized, Double-Blind, Dose-Ranging Study to Evaluate the Safety and Effectiveness of Eluxadoline in Pediatric Subjects (Aged 6 to 17 years) With Diarrhea-Predominant Irritable Bowel Syndrome

- A Randomized, Double-Blind Study to Confirm the Safety and Effectiveness of Eluxadoline in Pediatric Subjects (Aged 6 to 17 years) With Diarrhea-Predominant Irritable Bowel Syndrome

I concurred with above plan.

11. Other Relevant Regulatory Issues

Proprietary Names
DMEPA have completed review of the proposed proprietary name, (b) (4) on 09/05/2014, and have concluded that this name is acceptable, based on Sherly Abraham's review dated 09/05/2014.

On December 23, 2014, the sponsor submitted another proposed proprietary name, (b) (4) and request review. DMEPA have completed the review of the proposed proprietary name, (b) (4) on 02/03/2015 and have concluded that this name is unacceptable for the following reason: the proposed name, (b) (4) . The proposed

indication for this drug is for the treatment of irritable bowel syndrome with diarrhea (IBS-d). (b) (4) FDA informed the sponsor that the proposed proprietary name, (b) (4) is not acceptable 02/03/2015.

On February 12, 2015, the sponsor submitted a new proprietary name VIBERZI for approval. It is under review now.

Dr. Susan Leibenhaut is the Medical Officer from Good Clinical Practice Assessment Branch, Division of Clinical Compliance Evaluation, Office of Scientific Investigations. She concluded that 5 clinical investigator sites, the sponsor, and the CRO responsible for the IXRS were inspected for this NDA. Three clinical sites had the classification of NAI and two clinical sites had the classification of VAI with minor regulatory violations noted. For the sponsor and CRO inspections, the preliminary classifications are NAI. The studies appear to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications.

We chose sites for inspection on the basis of several factors including high enrollment, previous inspections, complaints, and efficacy results. The sponsor was inspected because this application is for a new molecular entity. The sponsor was inspected because of the central role of the interactive voice response system [IVRS] in these clinical trials.

Inspections at all clinical sites were unremarkable. One clinical site was identified that study personnel were entering data for the subjects. This clinical site was from Dr. Ana Lorena Lewy Alterbaum office. At this site, for Protocol 3001, 27 subjects were screened, 8 subjects were enrolled, and 6 subjects completed the study. Full source data was reviewed for all 8 enrolled subjects. For Protocol 3002, 9 subjects were screened, 5 subjects were enrolled and completed the study. Full source data was reviewed for 5 subjects in Protocol 3002. The inspection included review of informed consent documents (ICDs), enrollment logs, institutional review board (IRB) correspondence and approvals, sponsor correspondence, investigator agreements (1572s), financial disclosure, adverse event reports, electronic case report forms (e-CRFs), device accountability records, Interactive Voice Response System (IVRS) information, and source documents.

DSI found that there was no evidence of under-reporting of adverse events. No discrepancies were noted between the line listings and the source documents and data. A Form FDA 483 was issued for failing to follow the protocol and not reporting changes in research activity to the IRB prior to implementation. While the trial was ongoing, the monitors determined that study personnel were entering data for the subjects. When this was brought to the attention of the clinical investigator (CI), she removed the study staff, discussed the issues with the subjects, and instituted corrective actions. The FDA inspection confirmed these allegations by the sponsor and the corrective actions by the CI. In addition, Dr. Muldowney reviewed the efficacy results for this site and found that the site had 0 responders in either trial (8 patients in 3001

and 5 patients in 3002), therefore, I agreed with Dr. Muldowney that the site did not disproportionately contribute to the efficacy of eluxadoline.

I concurred with DSI's conclusion that the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the indication. I also concurred with DSI final overall conclusion the studies appear to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications.

12. Labeling

The applicant's proposed label included all the required sections and was appropriately formatted. The Applicant's proposed label was reviewed, and discussions regarding labeling recommendations are ongoing at the time of this review. The final approved labeling will be appended to the approval letter.

Dr. Tamal Chakraborti is the nonclinical pharmacology reviewer and has following labeling recommendations. I concurred with his recommendations.

8.1 Pregnancy

(b) (4)

Animal Data

Eluxadoline administered (b) (4) (about 51 and 115 times, respectively, the human AUC of 24 ng.h/mL after a single oral dose of 100 mg) and 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 of 24 ng.h/mL after a single oral dose of 100 mg).

13 Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year oral carcinogenicity studies have been conducted with eluxadoline in CD-1 mice at doses up to 1500 mg/kg/day (about 14 times the human AUC of 24 ng.h/mL after a single oral dose of 100 mg) and in Sprague Dawley rats at oral doses up to 1500 mg/kg/day (about 36 times the human AUC of 24 ng.h/mL after a single oral dose of 100 mg). Oral administration of eluxadoline for 104 weeks did not produce tumors in mice and rats.

Mutagenesis

Eluxadoline was negative in the Ames test, the chromosome aberration test in human lymphocytes, the mouse lymphoma cell (L5178Y/TK+/-) forward mutation test and the in vivo rat bone marrow micronucleus test.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I concur with Dr. Muldowney's recommendation that NDA 206940 for TRADENAME (eluxadoline) tablets be approved for the indication in adults for the treatment of irritable bowel syndrome with diarrhea (IBS-D).

The recommended dosage is 100 mg taken orally twice daily with food. For patients who have had a prior cholecystectomy or who are unable to tolerate the 100 mg dose secondary to adverse reaction, the recommended dosage is 75 mg taken orally twice daily with food.

Overall, I concur with Dr. Muldowney's conclusion that the benefits of eluxadoline outweigh the risks in the treatment of adult patients with irritable bowel syndrome with diarrhea (IBS-D), when used as labeled. The data in this NDA demonstrated eluxadoline is effective in adults for the treatment of IBS-D. The Applicant adequately characterized the safety profile of eluxadoline. The Full Prescribing Information, Medication Guide, and risk communication guide are sufficient to inform prescribers and patients of the risks of pancreatitis and hepatobiliary events related to sphincter of Oddi spasm.

Postmarketing surveillance with a focus on events of special interest is sufficient to monitor the safety profile of eluxadoline following its approval and marketing. A decision on the scheduling of eluxadoline will be made following further evaluation of the data that were submitted recently.

- Recommendation for other Postmarketing Requirements and Commitments

In addition to pediatric studies listed above, clinical pharmacology team recommends following phase 4 studies:

1) In –Vivo Study
   a) A dedicated renal impairment study. A reduced study design (where the sponsor can conduct the study in patients with ESRD not yet on dialysis and subsequently decide on the necessity of a study in patients with lower degree of renal impairment) as discussed at pre-NDA stage will be acceptable.

Rationale: A dedicated renal impairment study was not conducted in this submission.

2) In-Vitro Studies:
   a) In-vitro studies to adequately characterize the metabolism of eluxadoline in respect to various drug metabolizing enzymes. Depending on the results, further studies may be necessary.

Rationale: The in-vitro test systems used to evaluate the potential metabolism (human hepatocytes, microsomes and S9) of eluxadoline were not adequately characterized in respect to various phase 1 and 2 enzymes prior to the studies.

b) Further in-vitro studies to assess the in-vivo relevance of time-dependent inhibition of CYP3A4 by eluxadoline. Depending on the results, an in-vivo study may be necessary.

Rationale: Preliminary in-vitro data suggest time-dependent inhibition of CYP3A4 by eluxadoline at a concentration (50 uM) that can be achieved in the gut (Igut is estimated to be 400 μg/mL or 700 uM). Further in-vitro studies are necessary to allow an adequate assessment of in-vivo relevance of this interaction.

c) In-vitro study to estimate the IC50 (or Ki) value of eluxadoline toward P-gp and subsequently predict the in-vivo relevance of this interaction. Depending on the result, invivo study may be necessary.

Rationale: Inhibition potential of eluxadoline toward transporters was only evaluated at one concentration, 400 ng/mL (no inhibition was demonstrated), and thus, IC50 (or Ki) values were not determined in this submission. Although the systemic concentration of eluxadoline (Cmax is 2-4 ng/ml) is almost 100-fold lower than the tested concentration, the eluxadoline concentration in the gut (Igut is estimated to be 400 μg/mL) can be about 1000-fold higher than the tested concentration. Therefore, further assessment is necessary.

d) In-vitro study to evaluate the potential of eluxadoline to inhibit CYP2C8 and induce CYP2B6.

Rationale: Potential of eluxadoline to inhibit CYP2C8 or induce CYP2B6 was not assessed in this submission.

CMC has a phase 4 recommendation as below:

1) The applicant commits to re-evaluate the dissolution acceptance criterion after dissolution data from at least 30 lots of commercial drug products are available, or a maximum period of 1 year post-launch. Additionally, a 15 minute time-point will be added to the dissolution test at time of product release and in the stability protocol where profiles will be followed at 10, 15, 20 and 30 minutes. The final evaluation will include an assessment of whether the dissolution criterion of Q = (b) (4)% can be applied at 10-minutes or 15- minutes, instead of the 20-minute interval.

- Recommended Comments to Applicant

None.

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

/s/

RUYI HE
04/22/2015