CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206940Orig1s000

MEDICAL REVIEW(S)

Medical Officer Clinical Review Addendum: NDA 206940
Division of Gastroenterology and Inborn Error Products

BLA Number:	**206,940**
Established name:	**eluxadoline**
Trade Name:	**Viberzi**
Dosing Regimen:	**75 or 100mg twice daily with food**
Applicant:	**Furiex Pharmaceuticals, Inc**
Intended Population:	**Treatment of adults with diarrhea predominant irritable bowel syndrome (IBS-d)**
Submit Date:	**June 26, 2014**
PDUFA Goal Date:	**May 27, 2015**
Clinical Reviewer:	**Laurie Muldowney, MD**

1. Explanation of Need for Clinical Review Amendment

This document is an addendum to a clinical review completed and finalized in DARRTS on February 27, 2015. The purpose of this addendum is to correct several typographical errors noted in the original clinical review. In addition, the required financial disclosure template is included as Appendix 1. No substantive changes are being made in this addendum, and it is still the recommendation of this reviewer that eluxadoline 100mg be approved for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adult patients. It is also the recommendation of this reviewer that eluxadoline 75mg be approved for the treatment of IBS-D in adult patients status post cholecystectomy, for patients expected to have higher exposures to eluxadoline, (i.e., patients with mild or moderate hepatic impairment and patients receiving concomitant OATP1B1 inhibitors), and for patients who are unable to tolerate the 100mg dose. These recommendations are based on the Applicant's demonstration of an acceptable safety and efficacy profile for patients with IBS-D.

Three corrections to the original clinical review and the required financial disclosure template are provided below.

Correction 1:
Table 47 of the original application shows adverse events leading to treatment discontinuations from the pooled phase 2 and 3 studies, including eluxadoline 75mg, 100mg, and 200mg compared with placebo. This reviewer combined AEs of abdominal pain and abdominal pain upper which resulted in study drug discontinuation, under a single abdominal pain AE. There were 12 AEs of abdominal pain in the 75mg treatment arm which led to discontinuation and 15 in the 100mg treatment arm. In the original clinical review, the percent of patients with these AEs leading to discontinuation was incorrectly documented as 14.9% and 14.5%, respectively. The correct percentages are 1.5% and 1.4%, respectively. This is shown in the corrected Table 47 below.

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

	Number (%) of patients			
	Eluxadoline 75 mg BID N = 807	Eluxadoline 100 mg BID N = 1032	Eluxadoline 200 mg BID N = 171	Placebo BID N = 975
Number of patients with ≥ 1 AE leading to discontinuation	67 (8.3)	80 (7.8)	22 (12.9)	42 (4.3)
Abdominal Pain[a]	12 (1.5)	15 (1.4)	12 (7.0)	3 (0.3)
Constipation	9 (1.1)	15 (1.5)	4 (2.3)	3 (0.3)
Nausea	5 (0.6)	0	4 (2.3)	4 (0.4)
Headache	3 (0.4)	1 (0.1)	3 (1.8)	1 (0.1)
Dizziness	1 (0.1)	1 (0.1)	3 (1.8)	2 (0.2)
Vomiting	1 (0.1)	2 (0.2)	2 (1.2)	1 (0.1)
Fatigue	0	0	2 (1.2)	2 (0.2)
Dry Mouth	0	0	3 (1.8)	0
Somnolence	0	1 (0.1)	2 (1.2)	0
Pruritis	1 (0.1)	0	2 (1.2)	0

Source: Modified from Applicant ISS Amendment Table 2.49

[a] Abdominal pain includes both AEs of abdominal pain and abdominal pain upper which resulted in study drug discontinuation

Correction 2:

Similarly, Table 48 of the original clinical review included an overall summary of adverse events of abdominal pain from the pooled phase 2 and 3 data using a broad search of MedDRA terms for abdominal pain (abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness). As described above, using the broad search of MedDRA terms for abdominal pain, there were still 12 AEs of abdominal pain in the 75mg treatment arm which led to discontinuation and 15 in the 100mg treatment arm. The percent of patients with these AEs leading to discontinuation was incorrectly documented as 14.9% and 14.5%, respectively, in the original review. The correct percentages are 1.5% and 1.4%, shown below in an updated table. The number of AEs of abdominal pain leading to discontinuation was 3 (0.3%) in the placebo arm.

Table 48: Overall Summary of Adverse Events of Abdominal Pain, Pooled Phase 2 and 3 Analysis

	Number (%) of Patients		
AEs of Abdominal Pain	**Eluxadoline 75mg BID (N=807)**	**Eluxadoline 100mg BID (N=1032)**	**Placebo BID (N=975)**
Overall AEs of Abdominal Pain[a]	69	92	54
Leading to Discontinuation	12 (1.5)	15 (1.4)	3 (0.3)
Categorized as Serious[b]			
yes	3	3	0
no	66	89[b]	54
Categorized as Severe			
yes	4	13	6
no	65	79	48

[a] For the purposes of this analysis, this reviewer used a broad search of MedDRA terms for abdominal pain (abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness)

[b] Patients with more than one AE of abdominal pain categorized fitting into both serious and non-serious categories were listed only once as serious

[c] Patients with more than one AE of abdominal pain categorized with different severity were listed only once with their most severe AE of abdominal pain listed as severe or not severe

Correction 3:

Section 7.5.5. Drug-Drug Interactions summarizes GI adverse events occurring in patients who used loperamide rescue medication during the clinical study. The original review states that "Overall, 829 patients in the Safety Analysis Set from Studies IBS-3001 and IBS-3002 used at least 1 dose of rescue medications (272, 262, and 295 patients in the 75mg, 100mg, and placebo groups, respectively)." The Safety Analysis Set includes patients from the Phase 2 and 3 studies who received 75mg, 100mg, or placebo. This sentence should state:

Overall, 829 patients in the pooled Safety Analysis Set used at least 1 dose of rescue medications (272, 262, and 295 patients in the 75mg, 100mg, and placebo groups, respectively).

Appendix 1: Financial Disclosure Review Template

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 206940

Submission Date(s): June 26, 2014

Applicant: Furiex Pharmaceuticals, Inc

Product: eluxadoline (Viberzi)

Reviewer: Laurie Muldowney, MD

Date of Review: May 22, 2015

Covered Clinical Study (Name and/or Number): IBS-3001 and IBS-3002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: **959 investigators**		
Number of investigators who are sponsor employees (including both full-time and part-time employees): **0**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **0**		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): **n/a** Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) **0**		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[2] The disclosed information does not affect the approvability of the application.

[1] See [web address].
[2] See [web address].

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

/s/

LAURIE B MULDOWNEY
05/26/2015

DONNA J GRIEBEL
05/26/2015

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206940
Priority or Standard	Priority
Submit Date(s)	June 26, 2014
Received Date(s)	June 27, 2014
PDUFA Goal Date	May 27, 2015
Division / Office	Division of Gastroenterology and Inborn Error Products/Office of Drug Evaluation III
Reviewer Name(s)	Laurie Muldowney, MD
Review Completion Date	February 27, 2015
Established Name	Eluxadoline (JNJ-27018966)
(Proposed) Trade Name	TBD
Therapeutic Class	mixed mu opioid receptor (μOR) agonist/delta opioid receptor (δOR) antagonist
Applicant	Furiex Pharmaceuticals, Inc.
Formulation(s)	Immediate release oral tablet
Dosing Regimen	• 100 mg twice daily with food • 75mg twice daily with food

	for patients with prior cholecystectomy or who cannot tolerate the 100mg dose
Indication(s)	Treatment of adults with diarrhea predominant irritable bowel syndrome (IBS-d).
Intended Population(s)	Adults with IBS-d

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is the recommendation of this reviewer that eluxadoline 100mg be approved for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adult patients. It is also the recommendation of this reviewer that eluxadoline 75mg be approved for the treatment of IBS-D in adult patients status post cholecystectomy and for patients who are unable to tolerate the 100mg dose. These recommendations are based on the Applicant's demonstration of an acceptable safety and efficacy profile for patients with IBS-D.

1.2 Risk Benefit Assessment

Irritable bowel syndrome affects up to 20% of adults in North America, and diarrhea predominant IBS (IBS-d) accounts for approximately 1/3 of all cases[1]. While IBS-d is not a life threatening condition, its chronic relapsing nature has been shown to have a significant impact on patient quality of life and day-to-day functioning. Alosetron is the only FDA-approved therapy for IBS-d; however, its use limited to women with severe disease, and it is marketed under a restricted distribution REMS due to safety concerns related to serious complications of constipation and ischemic colitis. There is a clear need for additional treatment options for IBS-d, particularly for men with the condition, given the lack of approved therapies for this subgroup.

Efficacy: Two phase 3 clinical trials (IBS-3001 and IBS-3002) were conducted to support the efficacy claim for eluxadoline 100 mg BID and 75mg BID for the treatment of diarrhea and abdominal pain in men and women with diarrhea predominant irritable bowel syndrome (IBS-d). IBS-3001 and IBS-3002 were multicenter, multinational, randomized, double-blind, placebo-controlled, phase 3 studies which included 2425 adult patients with IBS-d in the intention-to-treat population for efficacy analyses. The design and conduct of both trials was identical through Week 26, including primary and secondary endpoints.

The pre-specified primary endpoint in both studies was the proportion of composite responders over the initial 12 week double-blind period. A patient was a composite responder if he or she met the daily response criteria, which required simultaneous improvement in both abdominal pain and stool consistency, for at least 50% of the days with diary entries during Weeks 1 – 12.

1 Wald A. Irritable Bowel Syndrome – Diarrhea. Best Pract & Res Clin Gastroenterol 2012;26:573-580

In Study IBS-3001, the proportion of composite responders over Weeks 1 – 12 was significantly higher in patients receiving eluxadoline 100mg compared to placebo (25.1% vs 17.1%, p = 0.004) and in patients receiving eluxadoline 75mg compared to placebo (23.9% vs 17.1%, p = 0.014). Similarly, in Study IBS-3002, the proportion of composite responders was significantly higher in both eluxadoline treatment arms compared to placebo (29.6% 100mg and 28.9% 75mg vs 16.2% placebo, p<0.001) over 12 weeks of treatment. In addition, the proportion of patients who were composite responders to eluxadoline 100mg or 75mg over each 4-week interval through Week 26 was higher than placebo in both studies, suggesting a durability of response. Results from a number of sensitivity analyses, including worst case scenario sensitivity analyses, were consistent with the primary analysis and support the efficacy of eluxadoline in the treatment of IBS-D.

The Applicant assessed a number of secondary endpoints, including:

- proportion of pain responders
- proportion of stool consistency responders
- IBS-Global symptom responder
- IBS-AR responder
- IBS-QOL responder

The proportion of stool consistency responders for the 75mg and 100 mg treatment groups in Studies IBS-3001 and IBS-3002 was significantly higher than placebo over the interval from Weeks 1 – 12. The proportion of pain responders for the 75mg and 100 mg treatment groups was higher than placebo in both studies; however, the differences did not reach statistical significance. Results of other secondary analyses generally favored eluxadoline, however, no adjustment for multiple comparisons was made for secondary analyses and statistical significance should not be claimed.

Finally, the primary endpoint, composite responder, as well as abdominal pain and stool consistency responders were analyzed for a number of subgroups, including gender, age, BMI. Most patients in Studies IBS-3001 and IBS-3002 were between 41 and 64 years of age (N = 668 and N = 601 in IBS-3001 and -3002, respectively), followed by 18 to 40 (N = 497 and N = 418) and then ≥ 65 (N = 115 and N = 126). When analyzing results by age, the response rates in the middle age group were comparable to the overall rates for the study, while the response rates in the younger age group were generally lower and for the older age group were generally higher, when compared to overall rates for the studies. The small sample sizes in these age groups make inferences challenging, however, and given that this was a post-hoc analysis and not controlled for multiplicity, this reviewer believes the data support that eluxadoline is effective across age groups. Importantly, subgroup analyses by gender support that eluxadoline is effective in both men and women, and the results of other subgroup analyses were consistent across a variety of subpopulations and support that eluxadoline is effective across a variety of subgroups.

In total, the evidence supports that eluxadoline is effective in the treatment of adult patients with IBS-d. The efficacy was demonstrated across a number of primary and secondary analyses, as well as across a variety of subgroups.

Safety: A total of 2562 subjects have received at least 1 dose of oral eluxadoline during the clinical development program, this included 2232 patients with IBS-D in controlled clinical trial. Overall incidence rates for adverse events (AEs) were comparable across treatment groups during Phase 2 and 3 studies (49.3% 75mg, 44.3% 100mg, 42.4% placebo). The most common AEs reported were within the GI disorders SOC, and constipation occurred in a higher percentage of patients in eluxadoline treatment arms (7.4% 75mg and 8.1% 100mg) than placebo (2.5%). The overall rates of serious AEs were low, and the proportion of patients with SAEs was similar across treatment arms (4.2% 75mg, 4.0% 100mg, 2.6% placebo).

Important risks identified during eluxadoline clinical development were pancreatitis and hepatobiliary spasm, often associated with Sphincter of Oddi (SO) dysfunction. Adjudicated SO spasm associated events occurred in 13 patients during Phase 2 and 3 studies (0.058%) and were predominantly seen in patients status post cholecystectomy or without a gallbladder (12 of 13 patients). SO spasm is an established class effect with μOR agonists, and the Applicant adequately addresses this risk through labelling and a risk minimization and communication plan.

There was a slightly higher incidence of abdominal pain in the eluxadoline treatment arms compared to placebo, early in the course of treatment, and these events occurred more frequently in patients in the 100mg treatment arm, compared with the 75mg treatment arm. This was particularly true in patients who were status post-cholecystectomy. The Applicant proposed that most of these AEs of abdominal pain resembled AEs described as sphincter of Oddi spasm and proposed marketing the 75mg dose for patients who have had a prior cholecystectomy or who cannot tolerate the 100mg dose. Given the 75mg was demonstrated to be effective and there is the potential for increased abdominal pain with the 100mg dose, particularly in patients with prior cholecystectomy, this reviewer believes this is an acceptable approach.

Other adverse events of special interest included severe complications of constipation, as these have been reported with alosetron to treat IBS-d. In addition, while eluxadoline is primarily locally acting, the Applicant assessed adverse events related to the pharmacologic class of eluxadoline (mixed mu opioid receptor (μOR) agonist and delta opioid receptor (δOR) antagonist), including events of fall, syncope, and road traffic accidents, and special considerations related to abuse and withdrawal potential. The Applicant did a thorough job of evaluating for these potential adverse events, and there was no evidence of an imbalance between treatment arms. There was also no indication of symptoms related to withdrawal on discontinuation of eluxadoline during

phase 2 or 3 studies. The Applicant commits to continue to evaluate adverse events of special interest on an ongoing basis through enhanced pharmacovigilance.

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. At the time of this review, a recommendation on the potential scheduling of eluxadoline had not yet been made by the Controlled Substance Staff (CSS). A final decision on scheduling will be made following approval of the product.

Summary: Overall, it is the assessment of this reviewer 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 Applicant adequately characterized the safety profile of eluxadoline, and 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 its approval.

See also Appendix 1: Benefit-Risk Assessment for additional information.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

After a complete safety review and analysis, this clinical reviewer does not believe a formal postmarketing Risk Evaluation and Mitigation Strategy (REMS) is required for eluxadoline. The Applicant provided a non-REMS risk minimization strategy which included the following goals:

- To inform prescribers of the risks of pancreatitis and hepatobiliary sphincter of Oddi spasm events and to educate them on appropriate patient selection in order to minimize the occurrence of these events.
- To closely monitor the safety profile after launch of TRADENAME with a focus on these events of special interest.

The Applicant's risk minimization strategy to inform patients and educate prescribers includes the Full Prescribing Information, as well as a Medication Guide and a risk communication guide.

Full Prescribing Information: The full Prescribing Information contains information about the risk messages related to pancreatitis and sphincter of Oddi Spasm in the Contraindications (eluxadoline is contraindicated in patients with a history of pancreatitis, sphincter of Oddi disease, or alcoholism); Warnings and Precautions (Instructs prescribers on the risk of SOD spasm, as well as the signs and symptoms and steps that should be taken, should a patient develop signs or symptoms consistent with the disease. Patients with a history of cholecystectomy are at increased risk); Adverse Events (describes AEs related to sphincter of Oddi spasm and pancreatitis from the clinical trials); Patient Counseling Information (informs patients of signs and symptoms of AEs related to sphincter of Oddi spasm).

Patient Medication Guide: A Medication Guide was prepared, which contains safety information for patients, including information on sphincter of Oddi spasm and pancreatitis. The Medication Guide includes information on the risks of therapy and instructs patients to call their healthcare provider and discontinue eluxadoline if they feel they may be experiencing any signs or symptoms of sphincter of Oddi spasm or pancreatitis. The Medication Guide will be provided to patients each time eluxadoline is dispensed.

Communication Plan: The Applicant will implement a Communication Plan that will target gastroenterologists and other practitioners who treat patients with IBS-D. The Communication Plan will include: a Dear Healthcare Professional Letter (sent within 30 days of launch and again 1 year after launch to gastroenterologists as well as primary care physicians and other healthcare practitioners who prescribe medicines approved for IBS), a Dear Professional Society Letter (sent within 30 days of launch and again 1 year after launch to the leadership of professional societies representing gastroenterologists and other practitioners who prescribe medicines or care for patients with IBS-D); and a Web site (Applicant will have a web site with information about the indication, safety, and efficacy of eluxadoline. The website will have links to information for prescribers and patients, the full prescribing information, Medication guide, and DHCP Letter.); and sales force training on risk messages.

In addition, the Applicant commits to evaluate adverse events of special interest on an ongoing basis. This will focus on events of special interest based on their occurrence in the development program (e.g., hepatobiliary or pancreatitis events) as well as events that were not seen in the clinical development program, but represent a theoretical risk based on the pharmacology of eluxadoline (e.g., complications of constipation and specific CNS adverse events).

Reviewer Comments: This reviewer does not believe a formal postmarketing Risk Evaluation and Mitigation Strategy (REMS) is required for eluxadoline. The non-REMS risk minimization strategy provided by the Applicant is acceptable.

1.4 Recommendations for Postmarket Requirements and Commitments

At the time of this review, Postmarket Requirements and Commitments are recommended with the approval of eluxadoline, however, these are still under discussion with the Applicant.

The Clinical Pharmacology review team recommends the following post marketing commitment (PMC) studies:

- Conduct a dedicated renal impairment study
- Conduct an in vivo DDI study with CYP3A4 substrate to evaluate the clinical relevance of eluxadoline's potential to inhibit CYP3A4 via mechanism based inhibition
- Conduct an in-vitro study to evaluate the potential of JNJ-27018966 to induced CYP2B6
- Conduct an in-vitro study to evaluate the potential of JNJ-27018966 to inhibit CYP2C8

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
- An Open-Label Safety Study of Eluxadoline in Pediatric Subjects (Aged 6-17 Years) With Diarrhea-Predominant Irritable Bowel Syndrome

The applicant has requested a Waiver of Pediatric Study for pediatric patients from birth to <4 and a Deferral of Pediatric Study for pediatric patients ≥ 6 to 17 years and 11 months.

In addition, the Applicant committed to the following enhanced postmarketing pharmacovigilance:

- Assess adverse events of special interest on an ongoing basis – this will focus on events of special interest based on their occurrence in the development program (e.g., hepatobiliary or pancreatitis events) as well as events that were not seen in the clinical development program, but represent a theoretical risk based on the pharmacology of eluxadoline (e.g., complications of constipation and specific CNS adverse events).

Reviewer Comment: We generally have waived requirements for pediatric studies of IBS treatments in children under the age of 6 due to the low IBS incidence in that age group. The final determination of pediatric waiver and deferral will be made upon

presentation to the Pediatric Research Committee (PeRC) as part of the review of the NDA for IBS-D. This reviewer agrees with the proposed enhanced pharmacovigilance.

2 Introduction and Regulatory 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 and is defined as recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with two or more of the following: improvement with defecation, onset associated with a change in frequency of stool, and onset associated with a change in form (appearance) of stool.[2,3,4] 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.[5]

The pathophysiology of IBS is complex and remains uncertain. Familial studies are conflicting, but most suggest a genetic susceptibility to IBS; associations with specific genes have not yet been identified.[6] 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).[7] Finally, psychosocial factors including daily stress may impact the manifestation of IBS related symptoms.

IBS is not a life-threatening condition; however, its 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.[8]

[2] Longstreth GF, Thompson WG, Chey WD, et al. Functional Bowel Disorders. *Gastroenterol* 2006;130:1480-1491.
[3] Saito YA, Schoenfeld P, Locke GR. The Epidemiology of Irritable Bowel Syndrome in North America: A Systematic Review. *Am J Gastroenterol* 2002;97:1910-1915.
[4] Camilleri M. Current and Future Pharmacological Treatments for Diarrhea-Predominant Irritable Bowel Syndrome. *Expert Opin Pharmacother* 2013;14(9):1151-1160.
[5] Wald A. Irritable Bowel Syndrome – Diarrhea. *Best Pract & Res Clin Gastroenterol* 2012;26:573-580.
[6] Saito YA, Petersen GM, Locke GR, et al. The Genetics of Irritable Bowel Syndrome. *Clin Gastroenterol Hepatol* 2005;3(11):1057-65.
[7] Drossman DA. The Functional Gastrointestinal Disorders and the Rome III Process. *Gastroenterology* 2006;130(5):1377-1390.
[8] Thompson WG, Longstreth GF, Drossman DA, et al. Functional Bowel Disorders and Functional Abdominal Pain. *Gut* 199;45(Suppl 2):1143-1147.

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.[9,10,11] Bile acid binders including cholestyramine 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.[3] 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 are 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. The guidance recommended including only patients who meet the subtype-specific Rome III IBS diagnostic criteria and who have sufficient clinical manifestations of IBS to make demonstration of a clinically meaningful improvement possible. In addition, since IBS symptoms are intermittent, randomized clinical trials of at least 12-weeks duration are usually recommended.[12]

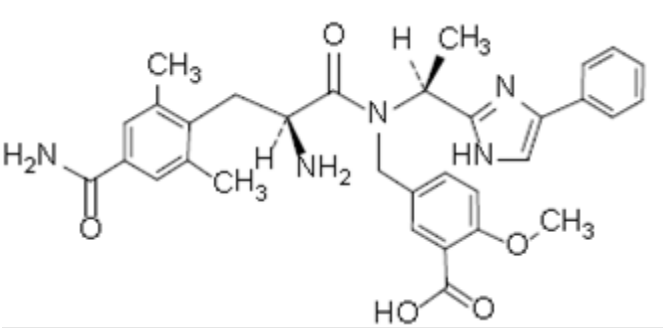
2.1 Product Information

Eluxadoline is a locally active, mixed mu opioid receptor (μOR) agonist and delta opioid receptor (δOR) antagonist. Eluxadoline has low oral bioavailability and acts through local action at opioid receptors within the GI tract.

Established name: eluxadoline

[9] Hovdenak N. Loperamide Treatment of the Irritable Bowel Syndrome. *Scand J Gastroenterol Suppl* 1987;130:81-84.
[10] Lavo B, Stenstam M, Nielsen AL. Loperamide in Treatment of Irritable Bowel Syndrom – A Double-Blind Placebo Controlled Study. *Scand J Gastroenterol Suppl* 1987;130:77-80.
[11] Talley NJ. Pharmacologic Therapy for the Irritable Bowel Syndrome. *Am J Gastroenterol* 2003;98(4):750-758.
12 FDA Guidance for Industry Irritable Bowel Syndrome – Clinical Evaluation of Drugs for Treatment. May 2012.

Structural formula:



Pharmacologic class:	Mixed mu opioid receptor agonist/ delta opioid receptor antagonist
Dosage Form and Strength:	100 mg immediate release oral tablet. Eluxadoline will be supplied as pink-orange to peach-colored 100 mg capsule shaped film-coated tablets and pale-yellow to light tan-colored 75 mg capsule shaped film-coated tablets.
Proposed indication:	Treatment of adults with diarrhea predominant irritable bowel syndrome (IBS-d).
Proposed dosing regimen:	100 mg twice daily with food; 75 mg twice daily with food for patients with prior cholecystectomy or who cannot tolerate the 100mg dose

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently approved treatments for IBS-d appear in **Table 1**.

Table 1: Currently approved treatments for IBS-D

Treatment	Drug Class	Indication	Main Safety Issues
Lotronex® (alosetron)	Selective serotonin 5-HT_3 antagonist	Women with severe diarrhea-predominant irritable bowel syndrome who have IBS symptoms longer than 6 months, no other anatomic or biochemical abnormalities of the GI tract, and who have not responded adequately to conventional therapy	Serious gastrointestinal adverse reactions including ischemic colitis and serious complications of constipation (obstruction, ileus, impaction, toxic megacolon, secondary bowel ischemia, perforation, and death). Lotronex is under restricted distribution as part of a REMS with ETASU[a].

Source: Reviewer's Table
[a] ETASU: Elements to Assure Safe Use

2.3 Availability of Proposed Active Ingredient in the United States

Eluxadoline is a new molecular entity (NME) that is not approved or marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Mu and delta opioid receptors regulate pain transmission, and systemically active agonists at both the μOR and δOR are analgesics. There are numerous FDA approved opioids with agonist activity at the μOR, including morphine and fentanyl. Common adverse reactions in patients taking opioids for pain relief include nausea and vomiting, drowsiness, itching, dry mouth, dizziness, sedation, decreased respiration, and constipation.

Importantly, these are systemically active opioids, whereas the Applicant proposes that eluxadoline has minimal oral bioavailability and acts locally in the GI tract. Loperamide is a locally acting μOR agonist. Loperamide is peripherally restricted and was found to have extremely low abuse potential in clinical studies designed to assess the abuse potential at high doses. Loperamide has been associated with significant GI sequelae, including ileus, megacolon, and toxic megacolon.

Submission specific safety concerns, based on safety issues with consideration to related drugs, are discussed in greater detail in **7.3.5 Submission Specific Primary Safety Concerns**.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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 Applicant 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 Applicant included an evaluation of efficacy at 12 weeks (FDA recommendation) and 26 weeks (EMA recommendation). In addition, there were multiple interactions between the Applicant and the FDA's Controlled Substance Staff regarding abuse potential study requirements. **Table 2** below summarizes pre-submission regulatory meetings and correspondence. A more detailed account of meetings and agreements is provided in **Appendix 5: Detailed Events of Pre-Submission Regulatory History**.

Table 2: 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: Reviewer's Table summarized from FDA Meeting Minutes

2.6 Other Relevant Background Information

There is no other relevant background information, except as discussed in other sections of this review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission quality and integrity are acceptable. The electronic application was well-organized and easy to navigate. The datasets were complete and navigable, however, the Applicant did not submit a Study Data Reviewer's Guide for their pivotal studies. In addition, the Applicant did not include an AE Treatment Emergent Flag or EPOCH variable in their datasets.

The application was originally submitted with incomplete safety data, as not all patients in IBS-3001 had completed the 52-week double blind treatment period. This was discussed with the Division during the pre-NDA meeting, and it was agreed that the application could be filed after the efficacy data was complete, but that the updated safety data would need to be provided by the 120-day safety update and would constitute a major amendment. The updated safety data was provided as agreed upon.

Reviewer Comments: The submission was of good quality. A Study Data Reviewer's Guide would have helped orient this reviewer to the data, particularly related to the handling of study drug misallocations in the Applicant's safety analyses. See Section 7.1 for additional details.

3.2 Compliance with Good Clinical Practices

The applicant includes a statement that all clinical trials were conducted in compliance with Good Clinical Practices (GCP). The application also included a debarment certification that the applicant did not use the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

The Office of Scientific Investigations (OSI) performed site investigations of 5 clinical sites which are summarized in **Table 3** below:

Table 3: Clinical Site Inspections

Principal Investigator/Location	Clinical Site Number	Protocol	Number of Subjects	Site Selection Rationale	Inspection Date(s)	Final Classification
Kutner, Mark Miami, FL	359	IBS-3001	60	Largest enroller in both studies; complaint history	Aug 18 to 28, 2014	NAI
	569	IBS-3002	90			
Lewy Alterbaum, Ana Lorena Cooper City, FL	363	IBS-3001	8	Participated in both studies.	November 10 to 13, 204	VAI
	842	IBS-3002	5			
Perez-Limonte, Leonel Miami, FL	371	IBS-3001	3	Outlier for efficacy.	September 24 to October 26, 2014	NAI
	541	IBS-3002	24			
Pineda-Velez, Armando Miami, FL	373	IBS-3001	22	Participated in both studies.	September 15 to 18, 2014	NAI
	832	IBS-3002	27			
Wilson, Scott Cumberland, RI	20	IBS-3001	12	Highest treatment effect, complaint and 2009 VAI, 56 INDs	September 2 and 10, 2014	VAI
CRO: (b) (4)	n/a	IBS-3001	n/a	n/a	(b) (4)	Pending (preliminary NAI)
		IBS-3002				
Sponsor: Furiex Pharmaceuticals, Inc.	n/a	IBS-3001	n/a	n/a	November 18 to 25, 2014	Pending (preliminary NAI)
		IBS-3002				

Source: reviewer created from OSI inspection summaries.
[a] VAI = Deviation(s) from regulation
[b] NAI = No deviation from regulation

Overview of Inspection Findings:

Clinical Site 359 (IBS-3001) and 569 (IBS-3002):
No significant regulatory violations were noted, and no Form FDA 483 was issued. The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the indication.

Clinical Site 363 (IBS-3001) and 842 (IBS-3002):

A Form FDA 483 was issued at this site for failing to follow the protocol and not reporting changes in research activity to the IRB prior to implementation. Specifically, while the trial was ongoing, the monitors determined that the study personnel were entering data for the subjects. When this was brought to the attention of the clinical investigator, she removed the study staff, discussed the issue with the patients, and instituted corrective action. The FDA confirmed the corrective actions were completed. The final classification was VAI, however, OSI assessed that the data generated by this site appeared acceptable in support of the indication.

Clinical Site 371 (IBS-3001) and 541 (IBS-3002):
There was no evidence of under-reporting of adverse events, and no discrepancies were noted between the line listings and the source documents and data. The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the indication.

Clinical Site 373 (IBS-3001) and 832 (IBS-3002):
There was no evidence of under-reporting of adverse events, and no discrepancies were noted between the line listings and the source documents and data. The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the indication.

Clinical Site 20 (IBS-3001):
A Form 483 was issued at this site. The site was found to be in general compliance with the instructions from the sponsor, with the exception that Subject 020021 was randomized in spite of having exclusion criterion of elevated lipase >2x ULN. This violation was noted by the sponsor while the study was ongoing. The final classification was VAI, however, OSI assessed that the data generated by this site appeared acceptable in support of the indication.

(b) (4)

There were no significant issues noted with the IXRS used in the study. No Form FDA 483 was issued, and the assessment by the inspector was that the studies appear to have been conducted adequately, and the data generated by this site may be used in support of the indication.

Furiex Pharmaceuticals, Inc.
The monitoring of investigators was adequate and the sponsor maintained adequate oversight. Data receipt and handling were adequate. The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the indication.

Reviewer comment: OSI inspection reports are complete, with the exception of 2 pending reports for (b) (4) *and Furiex Pharmaceuticals, though these were*

given preliminary NAI and no Form 483s were issued at these sites. Three (3) of 5 clinical sites inspected were classified as NAI. Site 20 was classified as VAI, for the reasons summarized above; however, this violation did not adversely affect data integrity. Site 363/482 was classified as VAI due to study personnel entering data for patients. The site inspector confirmed that corrective action was taken by the site investigator. While this violation has the potential to impact data integrity, the site enrollment was not a significant proportion of the overall study population (8 patients in IBS-3001 and 5 in IBS-3002). Furthermore, this site had 0 responders in either study, so it does not appear the site disproportionately contributed to the efficacy of eluxadoline. OSI recommended that data from the inspected sites can be used in support of the NDA. This reviewer agrees with the OSI assessment.

3.3 Financial Disclosures

The Applicant provided a single signed copy of FDA Form 3454 with an appended list of investigator names from each covered study. This certified that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). No FDA Form 3455s were provided, as no investigators reported financial arrangements.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Eluxadoline is an immediate release oral tablet supplied as 75mg and 100mg film-coated tablets. The 75mg tablets are pale-yellow to light tan-colored capsule shaped tablets with “FX75” debossed on one side. The 100mg tablets are pink-orang to peach-colored capsule shaped tablets with “FX100” debossed on one side.

The full chemical name of eluxadoline is 5-[[[(2S)-2-amino-3-[4-(aminocarbonyl)-2,6-dimethylphenyl]-1-oxopropyl][(1S)-1- (4-phenyl-1H-imidazol-2-yl)ethyl]amino]methyl]-2-methoxybenzoic acid.72

Eluxadoline has a molecular weight of 569.65 and a molecular formula of C32H35N5O5.

The drug product is composed of eluxadoline and the inactive ingredients listed in **Table 4** below.

Table 4: Drug Product Composition

Ingredient	Function	75 mg Tablet Amount (mg/tab)	100 mg Tablet Amount (mg/tab)	% w/w
Eluxadoline drug substance	Active substance	75	100	(b) (4)
Silicified MCC (b) (4) NF				(b) (4)
Colloidal silica, NF				
Mannitol, USP				
Crospovidone (b) (4) NF				
Magnesium stearate, NF				
(b) (4)				
Opadry II				
(b) (4)				
Coated Tablet Weight		**618 mg**	**824 mg**	----

Source: Applicant Description and Composition of the Drug Product, Table 2.3.P.1-1

(b) (4)

There are no major efficacy or safety issues from chemistry, which recommends approval. For more information see the Product Quality Reviews by Yichun Sun, PhD and Assad Noory, PhD.

4.2 Clinical Microbiology

This is an oral formulation. There are no major efficacy or safety issues from product quality microbiology. Reference is made to the Product Quality Microbiology Review.

4.3 Preclinical Pharmacology/Toxicology

The focus of the eluxadoline nonclinical program was to characterize its opioid receptor activity, assess the potential for opioid-related adverse effects, and characterize the toxicity profile. In vitro OR binding studies showed that eluxadoline is a potent μOR agonist and δOR antagonist, with weak kappa OR agonist activity. In rodent stress-induced diarrhea studies, eluxadoline normalized GI motility over a 20-fold dose range without completely preventing motility. This was in contrast with loperamide, which prevented GI motility completely at 3- to 4- fold the minimum effective dose.

The pharmacokinetics of eluxadoline were similar across species. Eluxadoline is absorbed rapidly after oral dose and has low bioavailability in mice, rats, and cynomolgus monkeys (≤ 0.83%). The toxicology of eluxadoline was characterized in single dose oral and intraperitoneal studies in mice and rats. In addition, repeat oral dose studies were conducted in mice (28 day and 3 month), rats (5 day, 28 day, 2 month, and 6 month), and monkeys (5, 7, and 28 day, 3 month, and 9 month). Oral administration was well-tolerated up to relatively high doses: 2000 mg/kg in rats for 6 months, 1500 mg/kg in rats and mice in carcinogenicity studies, and 200 mg/kg in cynomolgus monkeys for 9 months. The NOAEL for the 26-week GLP rat study was 2000 mg/kg/day, and the NOAEL for the 39-week GLP cynomolgus monkey study was 200 mg/kg/day, the highest dose administered in both studies. When administered IV, eluxadoline behaved as an opioid in rats and monkeys, and the systemic effects were reversed with naloxone. Eluxadoline was not shown to be genotoxic and did not produce any evidence of oncogenic effect in mice or rats at doses up to 1500 mg/kg/day. Finally, fertility and early embryonic development in rats were unaffected up to doses of 1000 mg/kg/day, and pre- and postnatal development were unaffected following daily administration of 1000 mg/kg/day. A summary of the toxicology program is shown in **Table 5** below.

Table 5: Summary of Toxicology Program for Eluxadoline

Study Type and Duration	Route of Administration	Species
Single dose toxicity	Oral and IP	Mouse and rat
Repeat dose toxicity		
5 and 7 day	Oral, SC, and Oral/SC[a]	Rat and monkey
1 month	Oral and Oral/SC	Mouse (oral only), rat and monkey
3 month	Oral and Oral/SC	Mouse (oral only), rat and monkey
6 month	Oral	Rat
9 month	Oral	Monkey
2 week	IV	Rat and monkey
Genotoxicity		
AMES	In vitro	Bacteria
Lymphoma	In vitro	Mouse
Chromosome aberration	In vitro	Human
Micronucleus	IP	Rat
Carcinogenicity		
104 week	Oral	Mouse and rat
Reproductive toxicity		
Fertility and early embryonic development	Oral	Rat
Embryofetal development	Oral and SC	Rat and rabbit
Pre- and postnatal development	oral	Rat
Juvenile toxicity		
1 month	Oral	Rat
Other		
Murine lymph node	Dermal	Mouse
Bovine cornea	In vitro	Bovine
Phototoxicity	In vitro	mouse

Source: Applicant's nonclinical overview
[a] oral/SC denotes studies done with concomitant oral and SC doses to increase systemic exposure

There are no major efficacy or safety issues from nonclinical, which recommends approval. For more information see the Nonclinical Review by Tamal Chakroborti, PhD.

4.4 Clinical Pharmacology

The Clinical Pharmacology review team found the information submitted to support this NDA to be acceptable with the following recommendations for post marketing commitment (PMC) studies:

1. Dedicated renal impairment study
2. In vivo DDI study with CYP3A4 substrate to evaluate the clinical relevance of eluxadoline's potential to inhibit CYP3A4 via mechanism based inhibition
3. In-vitro study to evaluate the potential of JNJ-27018966 to induced CYP2B6
4. In-vitro study to evaluate the potential of JNJ-27018966 to inhibit CYP2C8

For more detailed information see the Clinical Pharmacology Review by Dilara Jappar, PhD.

4.4.1 Mechanism of Action

Eluxadoline is a locally active, mixed mu opioid receptor (μOR) agonist/delta opioid receptor (δOR) antagonist. Eluxadoline acts locally, within the gastrointestinal (GI) tract, where the extensive expression of opioid receptors are believed to play a key role in regulating GI motility, secretion, and visceral sensation. Eluxadoline has demonstrated efficacy in normalizing GI transit and defecation in animal models of stress induced or post GI inflammation-altered GI function, as well as reversing hyperalgesic responses in an animal model of acute colitis-induced visceral pain.

4.4.2 Pharmacodynamics

Eluxadoline has low oral bioavailability, thus pharmacodynamics are assessed based on local action within the GI tract. A clear PK/PD relationship was not found in Phase 2 Study IBS-2001. The onset of eluxadoline's pharmacodynamic effects is rapid, as demonstrated by improvements in abdominal pain and stool consistency early in the course of treatment.

Pharmacodynamic studies assessing the impact of eluxadoline on CNS parameters (pupilometry, Bond-Lader Visual Analog scores, ARCI 49 assessment) showed no dose-related trends over time in change from baseline, supporting the lack of systemic effects with orally administered eluxadoline. These results were consistent with a clinical study in opioid abusers showing no significant changes in pupillary constriction or drug liking with doses up to 1000mg.

4.4.3 Pharmacokinetics

Eluxadoline has low oral bioavailability due to poor GI permeability and moderate hepatic first-pass extraction, involving OATP1B1-mediated hepatic uptake of eluxadoline. Co-administration with food lowers systemic exposures. The half-life of eluxadoline is approximately 5 hours, with high inter-subject variability. Eluxadoline shows dose-linearity across single oral doses from 30mg to 2000mg, and accumulation analyses after oral doses up to 500mg BID for 7 days showed no plasma accumulation of drug. Eluxadoline is not metabolized, and no metabolites were detected in plasma after oral administration of 1000mg eluxadoline. Biliary excretion accounts for over 80% of overall elimination, and renal excretion plays a minimal role in elimination.

Eluxadoline is not a substrate, inducer, or significant inhibitor of CYP enzymes in vitro in primary human hepatocytes and liver microsomes. Drug-drug interaction studies

indicate that eluxadoline is a substrate and weak inhibitor of the hepatic uptake transporter OATP1B1 and a substrate of OAT3 and MRP2.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 6. Overview of Clinical Development Program Supporting Efficacy of Eluxadoline for IBS-d

Study ID	Study Design	Study Population	Study Enrollment and treatment Arms	Primary Endpoint
IBS-2001	12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study	Adult patients with IBS-d based on Rome III criteria and who met baseline criteria for pain, stool consistency, and diary compliance during screening	807 total enrollment: 111 5mg BID, 174 25mg BID, 176 100mg BID, 174 200mg BID, 172 placebo BID	Clinical response defined as meeting BOTH IBS-d improvement-from-baseline criteria: average daily pain score over the past week improved by ≥ 30% and at least 2 points and BSS consistency score of 3 or 4 on > 66% of reported days in past week
IBS-3001	52-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study	Adult patient with IBS-d based on Rome III criteria and who met baseline criteria for pain, stool consistency, and IBS-d global symptom score and diary compliance during the week prior to randomization	1282 total enrollment: 429 75 mg BID, 426 100 mg BID, 427 placebo BID	Composite response (simultaneous improvement in abdominal pain and BSS scores for more than 50% of the days with diary entries) through week 12
IBS-3002	26-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study with 4-week, single-blind withdrawal period		1146 total enrollment: 381 75 mg BID, 383 100 mg BID, 382 placebo BID	

Source: Reviewer's Table Summarized from Applicant's Integrated Summary of Efficacy

5.2 Review Strategy

For this NDA submission, Phase 3 Clinical Trials IBS-3001 and -3002 were reviewed in detail. Details of the study design and conduct for each trial are contained in Section 5, and study results are discussed in Sections 6 (efficacy) and 7 (safety). Study IBS-2001 is considered supportive and data is primarily used in the review of safety and analysis of clinical information relevant to dosing recommendations. .

5.3 Discussion of Individual Studies/Clinical Trials

General Information Regarding Controlled Efficacy Studies
The placebo-controlled efficacy studies (IBS-3001 and IBS-3002) were identical studies through Week 26, including primary and secondary objectives, entry criteria, treatment, study visits and procedures, control procedures, primary and secondary efficacy endpoints, statistical plan, and protocol amendments. After Week 26, study IBS-3002 included a 4-week blinded withdrawal phase, while IBS-3001 included an additional 26-week double blind safety assessment. Protocol items that differed between the two studies are highlighted below.

5.3.1 Protocol Summary

Title
Study IBS-3001
A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-27018966 in the Treatment of Patients with Diarrhea-Predominant Irritable Bowel

Study IBS-3002
A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-27018966 in the Treatment of Patients with Diarrhea-Predominant Irritable Bowel

Study Overview
Study IBS-3001
Study IBS-3001 was a multicenter, multinational, randomized, double-blind, placebo-controlled, phase 3 study to evaluate the efficacy, safety and tolerability of eluxadoline in the treatment of 1282 adult patients with diarrhea-predominant irritable bowel syndrome. IBS-3001 included a 52-week double blind treatment period, with efficacy assessments at 12 and 26 weeks and continuation to Week 52 for long term double blind safety data. This study was conducted at 295 sites in the United States (269 sites), Canada (9 sites), and the United Kingdom (17 sites). The first subject was prescreened on 29May2012 and the last patient completed his/her last visit on 29 July 2014.

Study IBS-3002
Study IBS-3002 was a multicenter, multinational, randomized, double-blind, placebo-controlled, phase 3 study to evaluate the efficacy, safety, and tolerability of eluxadoline in the treatment of 1146 adult patients with diarrhea-predominant irritable bowel syndrome. IBS-3002 included a 26-week double blind treatment period and 4-week single-blinded withdrawal period. This study was conducted at 261 sites in the United States (245 sites), Canada (7 sites), and the United Kingdom (9 sites). The first subject was prescreened on 29May2012 and the last patient completed his/her last visit on 09January2014.

Table 7: Study Centers by Country:

Location	Study IBS-3001		Study IBS-3002	
	Number of Centers	Number of Patients Enrolled	Number of Centers	Number of Patients Enrolled
United States	269	1214	245	1098
Canada	9	25	7	32
United Kingdom	17	43	9	16

Source: Reviewer's Table summarized from Sponsor's Integrated Summary of Efficacy

Primary Objectives:
IBS-3001:

- To evaluate the clinical response of patients with IBS-d to eluxadoline relative to placebo
- To evaluate the overall safety and tolerability of eluxadoline in the treatment of IBS-d for up to 52 weeks

IBS-3002:

- To evaluate the clinical response of patients with IBS-d to eluxadoline relative to placebo

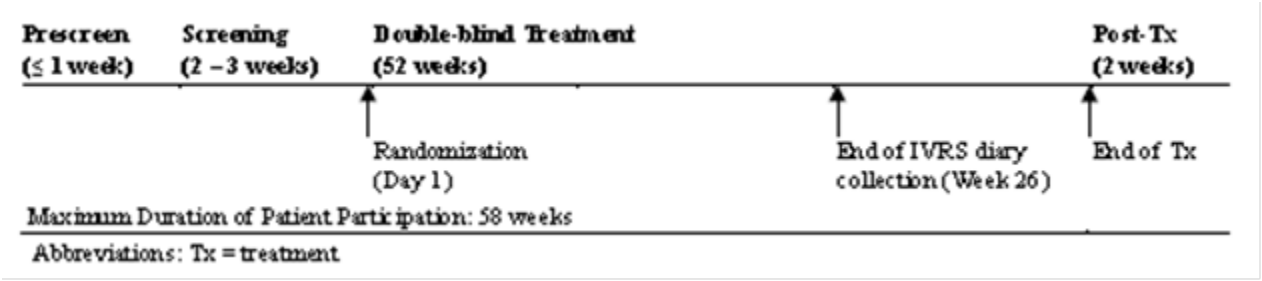
Secondary Objectives:
IBS-3001 and -3002

- To further evaluate the treatment effect of eluxadoline relative to placebo based on patient reports of IBS-d symptoms (abdominal pain, abdominal bloating, stool consistency, global symptom scores, adequate relief), bowel functioning, and quality of life

Study Design
IBS-3001
IBS-3001 consisted of a pretreatment phase, including an up to 1-week prescreening period and an up to 3-week screening period, a 52-week double-blind treatment phase, and a 2-week post-treatment follow-up period. The total planned duration was not more

than 58 weeks for each patient. Daily electronic diary data was collected, and efficacy assessments were conducted, through Week 26. Extraction of efficacy and safety data for statistical analysis was conducted when all patients had completed 26 weeks of treatment. The continuation of treatment through Week 52 was to allow for continued assessment of long-term safety with placebo control, and investigative site staff and patients remained blinded through Week 52.

Figure 1: IBS-3001 Clinical Study Design

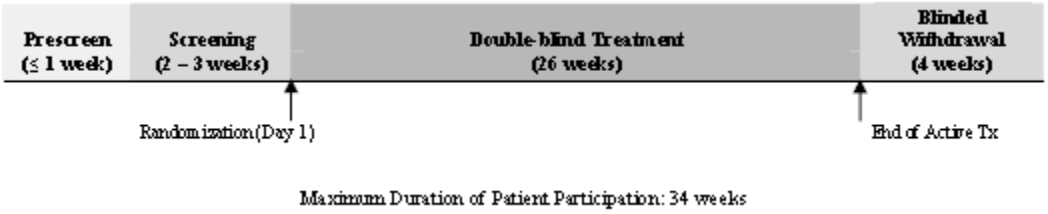


Copied and electronically reproduced from Applicant's submission, Study IBS-3001 Clinical Study Report, Figure 9-1.

IBS-3002

IBS-3002 consisted of a pretreatment phase identical to study IBS-3001 (up to 1-week prescreening period and an up to 3-week screening period), a 26-week double-blind treatment phase, and a 4-week blinded withdrawal phase. The total planned duration was not more than 34 weeks for each patient. Daily electronic diary data was collected through Week 30, however, primary and key secondary efficacy assessments were conducted through Week 26. The 4-week blinded withdrawal allowed for evaluation of rebound effects on study drug discontinuation.

Figure 2: IBS-3002 Clinical Study Design



Copied and electronically reproduced from Applicant's submission, Study IBS-3002 Clinical Study Report, Figure 9-1

5.3.2 Key Inclusion Criteria

IBS-3001 and -3002

1. Male or female aged 18 to 80 years, inclusive, at Prescreening

2. Diagnosis of IBS with a subtype of diarrhea defined by the Rome III criteria as loose (mushy) or watery stools ≥25% and hard or lumpy stools <25% of bowel movements
3. Colonoscopy performed:
    a. Within 10 year prior to prescreening if they are at least 50 years of age
    b. Since the onset (if applicable) of any of the following alarm features:
        i. Documented weight loss within the past 6 months;
        ii. Nocturnal symptoms;
        iii. Familial history of colon cancer; or
        iv. Blood mixed with their stool (excluding any blood from hemorrhoids)
4. Average of worst abdominal pain scores in the past 24 hours of >3.0 on a 0 to 10 scale over the week prior to randomization.
5. Average stool consistency score (BSS) of ≥5.5 and at least 5 days with a BSS score ≥5 on a 1 to 7 scale over the week prior to randomization.
6. Average daily IBS-d global symptom score of ≥2.0 on a 0 to 4 scale over the week prior to randomization.
7. Completed electronic diary on at least 6 of the 7 days during the week prior to randomization AND at least 11 of the 14 days during the 2 weeks prior to randomization.
8. Patient has not used any loperamide rescue medication within 14 days prior to randomization.
9. Must maintain stable diet and lifestyle throughout study. Stable antidepressants (i.e., ≥ 3 months prior to prescreening) and as needed benzodiazepines for anxiety are acceptable. Patients may be taking medications for the treatment of allergies, chronic medical conditions, and migraine headaches, with the exception of opioids for acute treatment of migraines.
10. Premenopausal women must be surgically sterile, abstinent, or practicing effective birth control

5.3.3 Key Exclusion Criteria

IBS-3001 and -3002

1. IBS with a subtype of constipation, mixed IBS, or unsubtyped IBS by the Rome III criteria
2. History of inflammatory or immune-mediated GI disorders including inflammatory bowel disease and celiac disease
3. History of diverticulitis within 3 months prior to Prescreening
4. History of intestinal obstruction, stricture, toxic megacolon, GI perforation, fecal impaction, gastric banding, bariatric surgery, adhesions, ischemic colitis, or impaired intestinal circulation
5. Any of the following surgical history:

   a. Cholecystectomy with ANY history of post cholecystectomy biliary tract pain. Patients who had a successful cholecystectomy with no post-operative biliary tract pain are candidates for the study;
   b. Any abdominal surgery within the 3 months prior to Prescreening;
   c. Major gastric, hepatic, pancreatic, or intestinal surgery (appendectomy, hemorrhoidectomy, or polypectomy greater than 3 months post-surgery are allowed)
6. History of cholecystitis within 6 months before Prescreening
7. History of pancreatitis of any etiology or biliary duct disease, excluding a history of gallstones, history of Sphincter of Oddi dysfunction
8. Elevated serum lipase >2 times the upper limit of normal at Prescreening
9. History or current evidence of laxative abuse
10. ALT/AST >3 times the upper limit of normal or total bilirubin >3 mg/dL, with the exception of Gilbert's syndrome, at Prescreening
11. History of a cardiovascular event within 6 months prior to Prescreening.
12. Unstable renal, hepatic, metabolic, or hematologic condition.
13. History of malignancy within 5 years before Prescreening, history of HIV infection
14. History of DSM-IV-TR–defined substance dependency, excluding nicotine and caffeine, within 2 years prior to Prescreening.
15. History of alcohol abuse or binge drinking
16. Known lactose intolerance
17. History of microbiologically documented lower GI infection within 3 months
18. Uncontrolled hypertension
19. Abnormal thyroid function test unless clinically euthyroid due to thyroid supplement
20. Hemoglobin <10 g/dL for women and <12 g/dL for men at Prescreening
21. Use of 5HT3 antagonists (e.g., alosetron) within 14 days of Prescreening
22. Use of aspirin or aspirin-containing medications or nonsteroidal anti-inflammatory drugs for the symptoms of IBS, within 14 days of randomization.
23. Current (within 14 days of randomization) or expected use of any narcotic or opioid containing agents, docusate, enemas, GI preparations (including antacids containing aluminum or magnesium, antidiarrheal agents, antinausea agents, antispasmodic agents, bismuth, or prokinetic agents)
24. Current (within 28 days of randomization) or expected use of rifaximin or other antibiotics (with the exception of topical antibiotics or a 1-day course with an antibiotic).
25. Unable to swallow solid, oral dosage forms
26. Received an investigational drug or used an investigational medical device within 30 days or was currently enrolled in an investigational study
27. Previously received investigational drug in a study of eluxadoline
28. Planned elective surgery during study.
29. Pregnant or breastfeeding
30. Any condition that, in the opinion of the Investigator, would compromise the well-being of the patient or the study

31. Patient was an employee of the Investigator or study center with direct involvement in the proposed study

5.3.4 Study Medication, Concomitant Medications

Treatment

IBS-3001

Patients were randomly assigned 1:1:1 to 1 of 3 treatment groups. Randomization was stratified by country.

- Group 1: eluxadoline 75 mg oral tablets BID
- Group 2: eluxadoline 100 mg oral tablets BID
- Group 3: matching placebo oral tables BID

Patients in each treatment group received kits containing 4 weeks' worth of study drug. Each 1-week wallet within the kit contained a total of 32 tablets, sufficient for 7 + 1 day of dosing. The study drug was packaged in a double-dummy fashion and patients received 2 tablets at each administration and continued double-blind study drug for 52 weeks. Patients were instructed to take the study drug twice daily and to swallow the study drug whole with liquid. Treatment compliance was assessed at the study centers by pill count.

IBS-3002

As described for IBS-3001, patients were randomly assigned 1:1:1 to 1 of 3 treatment groups. Randomization was stratified by country.

- Group 1: eluxadoline 75 mg oral tablets BID
- Group 2: eluxadoline 100 mg oral tablets BID
- Group 3: matching placebo oral tables BID

Patients in each treatment group received kits containing 4 weeks' worth of study drug. Each 1-week wallet within the kit contained a total of 32 tablets, sufficient for 7 + 1 day of dosing. During the first 12 weeks of double-blind treatment, patients were dispensed 1 kit at visits and from Week 12 through Week 26, two kits were dispensed. The study drug was packaged in a double-dummy fashion and patients received 2 tablets at each administration and continued double-blind study drug for 26 weeks. At the Week 26 visit, all patients were to be assigned kits with single-blind placebo. Patients were instructed to take the study drug twice daily and to swallow the study drug whole with liquid. Treatment compliance was assessed at the study centers by pill counts.

Prior and Concomitant Therapy:

IBS-3001 and -3002

All prescription medications, herbal products, vitamins, minerals, and OTC medications taken within 2 weeks prior to randomization were recorded as prior therapy. All medications taken after randomization and through Week 30 visit were recorded as

concomitant therapy. The following medications were prohibited as prior or concomitant therapy:

- $5HT_3$ antagonists (e.g., alosetron), prohibited within 14 days of Prescreening
- Aspirin or aspirin-containing medications or NSAIDs, when taken specifically for IBS within 14 days of randomization
- Narcotics, opioid-containing agents, or tramadol prohibited within 14 days of randomization
- Docusate, enemas, or GI preparations (antacids containing aluminum or magnesium, anti-diarrheal agents [except loperamide rescue medication after randomization], antinausea agents, antispasmodic agents, bismuth, or prokinetic agents), prohibited within 14 days of randomization
- Rifaximin prohibited within 28 days of randomization

Stable doses of antidepressants or medications to treat allergies, chronic medical conditions, or migraine headaches were permitted as prior and concomitant medications, except those listed above.

Loperamide was prohibited during the 3-week screening period. During the double-blind treatment period and blinded withdrawal, loperamide rescue medication was permitted for the acute treatment of uncontrolled diarrhea. Loperamide 2 mg every 6 hours was permitted with the following restrictions:

- No more than 8 mg over a continuous 24-hour time period
- No more than 14 mg over a continuous 48-hour time period
- No more than 22 mg over a continuous 7-day period

Patients recorded loperamide rescue use in their electronic diaries. A notification was automatically generated to alert investigator if a patient used more than the allowed amount of loperamide.

5.3.5 Study Visits and Procedures

Prescreening and Screening Period:
IBS-3001 and -3002
The schedule of events and study procedures for the prescreening and screening period is provided in **Table 8** below.

Table 8: Pretreatment Time and Events Schedule, IBS-3001

Period:	Prescreening	Screening
Week:	- 3	- 2
Study Procedures		
Informed consent	X	
Inclusion/exclusion criteria	X	X[d]
Demographics	X	
Medical history	X	X
Prior therapy[a]	X	X
Height	X	
Vital signs (pulse, rr, bp)	X	X
Physical examination	X	
Pregnancy Test[b]	X	
TSH	X	
Serum chemistry, hematology	X	
Abdominal pain/discomfort/bloating scores, BSS, IBS-d global symptom score, bowel functioning[c]		X
Instruct patients on electronic diary (IVRS)		X[e]

Source: Applicant Clinical Study Protocol, Table 6-1, IBS-3001
[a] any medications taken within 2 weeks prior to randomization should be recorded as prior therapy
[b] A serum pregnancy test will be performed for all women unless they are surgically sterile or documented history of postmenopausal status.
[c] Patients will be required to access an electronic diary (IVRS) each evening to record the items listed.
[d] Inclusion/exclusion criteria will be re-verified at Screening.
[e] Patients will be instructed on the importance of calling into the IVRS daily. Additionally, patients will be instructed on recording their use of loperamide rescue medication.

During prescreening and following signing of the informed consent document, patients underwent prescreening assessments and procedures, and the investigator assessed all inclusion/exclusion criteria to determine patient eligibility, with the exception of those related to IVRS criteria. Eligible patients entered a 2-week screening period, during which time they were to complete a daily electronic diary (via IVRS or IWRS) related to their IBS-d symptoms, bowel functioning, and loperamide use. At the completion of the screening period, the investigative sites were notified by the IVRS whether a patient met the IVRS criteria for randomization. Patients who met all of the following criteria were immediately randomized into the double-blind treatment phase:

- compliant in completing the screening diary on a daily basis on at least 6 of the 7 days during the week prior to randomization AND on at least 11 of the 14 days during the 2 weeks prior to randomization, and
- have an average of worst abdominal pain score in the past 24 hours of >3.0 on a 0 to 10 scale over the week prior to randomization, and
- have an average daily stool consistency score (BSS) of ≥5.5 and at least 5 days with a BSS score ≥5 on a 1 to 7 scale over the week prior to randomization, and

- have an average daily IBS global symptom score of ≥2.0 over the week prior to randomization, and
- who have not used any loperamide rescue medication in the 2 weeks prior to randomization

Patients who did not meet all 5 criteria were permitted an additional week of screening time (total 3 weeks) in which to satisfy all the criteria.

Double Blind Treatment Period:

IBS-3001

Patients in IBS-3001 had study visits throughout the 52 week treatment period at Weeks 2, 4, 8, 12, 18, 26, 36, 44, and 52. During the first 26 weeks of the double-blind treatment phase, patients were to record their daily IBS-d symptoms and information related to bowel functioning and loperamide use via the IVRS, preferably at the same time each day. In addition, once per week during the IVRS call, patients documented whether they were experiencing adequate relief of symptoms.

Efficacy assessments for determination of clinical response were conducted through 26 weeks, with the primary endpoint through 12 weeks for FDA and 26 weeks for EMA, respectively. Investigative site staff and patients remained blinded through Week 52 (for safety assessment); however, investigators were to receive automatic notifications from the IVRS as follows:

- Immediately if a patient has 4 consecutive days of no bowel movement as verified by non-missing IVRS entries (i.e., IVRS-confirmed constipation)
- Immediately if a patient exceeds the allowable amount of loperamide rescue medication use as verified by IVRS entries
- Periodically (i.e., once per week) to inform Investigators of patients' compliance in completing the daily diary

Safety assessments during the treatment phase included monitoring of adverse events, clinical laboratory assessments, vital signs, ECGs, and physical examination findings. The Subjective Opiate Withdrawal Scale (SOWS) was used to assess potential withdrawal symptoms throughout the study.

The schedule of events and study procedures for the double-blind treatment period are included in **Table 9** below.

Table 9: Treatment Phase Time and Events Schedule, IBS-3001

Phase	Baseline	Double Blind Treatment									Follow-up
Week	1(Day 1)	2	4	8	12	18	26	36	44	52 (end of tx/early withdrawal)[h]	54
Visit Windows:	--	± 2 days	± 2 days	± 3 days	± 3 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days
Study Procedures:											
Study Drug Administration											
Dispense Study Drug	X[a]		X	X	X	X	X	X	X		
Drug Accountability		X	X	X	X	X	X	X	X	X	
Safety/Efficacy/Patient-Reported Outcomes											
Abdominal pain/discomfort/bloating scores, BSS, IBS-d global symptom score, bowel functioning[b]	X	X	X	X	X	X	X				
IBS-AR[c]		X	X	X	X	X	X				
IBS-QoL[d]	X		X	X	X	X	X	X	X	X	
Weight	X									X	X
Vital signs (pulse, rr, bp)	X	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram	X				X		X			X	X
Physical examination	X				X		X			X	X
Serum chemistry, hematology[e]	X		X	X	X	X	X	X	X	X	X
Subjective Opiate Withdrawal Scale										X	
Pregnancy test[f]	X	X	X	X	X	X	X	X	X	X	
Ongoing Review											
Medical history	X										
Concomitant therapy[g]	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X

Review electronic diary notifications	X	X	X	X	X	X	X				

Source: Table 6-2, Applicant Clinical Study Protocol, IBS-3001

[a] Eligible patients will be dispensed in accordance with their randomly assigned treatment. Study drug was not dispensed until all other procedures were performed.

[b] Patients were required to access an electronic diary each evening to record daily stool consistency, worst abdominal pain/discomfort/bloating in the past 24 hours, their IBS-d global symptom score in the past 24 hours, and to report information related to their bowel functioning (X on schedule are to remind investigators that this will be an ongoing activity)

[c] Once per week patients were asked if they have experienced adequate relief of IBS symptoms during IVRS call

[d] IBS-QoL was to be completed during the patients scheduled visit, prior to all other evaluations

[e] lipase and triglycerides were to be assessed as part of serum chemistry at Baseline. Unscheduled blood draws for lipase and triglycerides were to be performed for any patients with confirmed or suspected AEs of pancreatitis. An increase in ALT/AST to > 3xULN should be followed by repeat testing within 48 – 72 hours of ALT, AST, alk phos, and tbili.

[f] pregnancy tests were to be performed unless patients are surgically sterile or there is a documented history of postmenopausal status.

[g] This includes assessment of loperamide use which is also recorded by the patient in the daily telephone diary for the first 26 weeks.

[h] End of treatment/early withdrawal evaluations were to be performed for patients who complete through Week 52 or who are withdrawn from the study. A patient who discontinues should return to complete the early withdrawal assessments as soon as possible after stopping study drug.

Post-treatment follow up (Week 54)
Patients who completed the study through week 52 were to return to the clinic for a post-treatment follow-up assessment. The schedule of events and study procedures for the post-treatment follow up are included in **Table 9** above.

IBS-3002
The treatment phase was identical through Week 26, however, IBS-3002 ended at Week 30 following a blinded withdrawal. During the withdrawal period, all patients received single-blind placebo and were to continue to access the IVRS every day to record their IBS-d symptom data and information related to their bowel functioning and loperamide use. The Time and Events schedule for IBS-3002 is shown in **Table 10** below.

Table 10: Treatment Phase Time and Events Schedule, IBS-3002

Phase	Baseline	Double Blind Treatment								Blinded Withdrawal
Week	1(Day 1)	2	4	8	12	18	26	36	44	30 (end of tx/early withdrawal)[h]
Visit Windows:	--	± 2 days	± 2 days	± 3 days	± 3 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days
Study Procedures:										
Study Drug Administration:										
Dispense Study Drug	X[a]		X	X	X	X	X	X	X	
Drug Accountability		X	X	X	X	X	X	X	X	X
Safety/Efficacy/Patient Reported Outcomes										
Abdominal pain/discomfort/bloating scores, BSS, IBS-d global symptom score, bowel functioning[b]	X	X	X	X	X	X	X			X
IBS-AR[c]		X	X	X	X	X	X			X
IBS-QoL[d]	X		X	X	X	X	X	X	X	X
Weight	X									X
Vital signs (pulse, rr, bp)	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram	X				X		X			X
Physical examination	X				X		X			X
Serum chemistry, hematology[e]	X		X	X	X	X	X	X	X	X
Subjective Opiate Withdrawal Scale										X[i]
Pregnancy test[f]	X	X	X	X	X	X	X	X	X	X
Ongoing Review:										
Medical history	X									
Concomitant therapy[g]	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X
Review electronic diary notifications	X	X	X	X	X	X	X			

Source: Table 6-2, Applicant Clinical Study Protocol, IBS-3002

[a] Eligible patients will be dispensed in accordance with their randomly assigned treatment. Study drug was not dispensed until all other procedures were performed.
[b] Patients were required to access an electronic diary each evening to record daily stool consistency, worst abdominal pain/discomfort/bloating in the past 24 hours, their IBS-d global symptom score in the past 24 hours, and to report information related to their bowel functioning (X on schedule are to remind investigators that this will be an ongoing activity)
[c] Once per week patients were asked if they have experienced adequate relief of IBS symptoms during IVRS call
[d] IBS-QoL was to be completed during the patients scheduled visit, prior to all other evaluations
[e] lipase and triglycerides were to be assessed as part of serum chemistry at Baseline. Unscheduled blood draws for lipase and triglycerides were to be performed for any patients with confirmed or suspected AEs of pancreatitis. An increase in ALT/AST to > 3xULN should be followed by repeat testing within 48 – 72 hours of ALT, AST, alk phos, and tbili.
[f] pregnancy tests were to be performed unless patients are surgically sterile or there is a documented history of postmenopausal status.
[g] This includes assessment of loperamide use which is also recorded by the patient in the daily telephone diary for the first 26 weeks.
[h] End of treatment/early withdrawal evaluations were to be performed for patients who complete through Week 52 or who are withdrawn from the study. A patient who discontinues should return to complete the early withdrawal assessments as soon as possible after stopping study drug.
[l] SOWS will only be completed at early withdrawal for patients who discontinue from the study prior to completion of the double-blind treatment period at Week 26. Patients who complete the blinded withdrawal period will not be required to complete the SOWS at Week 30

.

5.3.6 Control Procedures

Randomization
IBS-3001 and -3002
The randomization schedule was generated using the SAS software, and the schedule was sequestered until the study was unblinded. Patients were randomly assigned 1:1:1 to 1 of the 3 treatment groups. Randomization was stratified by country.

Randomization was via a central randomization interactive voice response system (IVRS)/interactive web response system (IWRS). Study sites accessed the IVRS/IWRS to execute each randomization, after a patient had met all prerequisites and had completed all Day 1 scheduled procedures. Patients were assigned a unique patient number by the randomization system which was not to be reused, even if the patient withdrew before receiving any study drug.

Placebo Control
IBS-3001 and -3002
This was a placebo-controlled trial. The investigational product was supplied as film-coated, white to off-white tablets containing 75 mg or 100 mg of active drug. Placebo tablets were supplied as matching tablets containing the same excipients. Drugs were packaged in a double-dummy fashion and patients received 2 tablets at each administration.

Blinding
IBS-3001 and -3002
This was a double-blind trial. All patients, investigators, and study site personnel were unaware of the treatment assignments for the patients. Should a medical emergency occur, the blind could be broken. Furiex unblinded selected SAEs that met the criteria for expedited reporting.

Data Management
IBS-3001 and -3002
Study data were entered from the source documents into an electronic data capture (EDC) system by study site personnel within 48 hours of completing the patients' visits. Principle Investigators (or authorized Sub investigators) are responsible for approval of the entered/corrected data. The clinical research associates will visit each study site, at a preplanned frequency, to review eCRFs for completeness and accuracy. Any discrepancies noted between source documents and eCRFs will be entered as a discrepancy in the EDC system. Data from eCRFs and other external data sources were entered into a clinical database. Quality control and data validation procedures were applied to ensure the validity and accuracy of the clinical database.

5.3.7 Outcome Measurements

Primary Efficacy Endpoint
IBS-3001 and -3002

- Proportion of composite responders over the initial 12 week double-blind period. A patient was a composite responder if he or she met the daily response criteria for at least 50% of the days with diary entries during Weeks 1 – 12. A patient was a daily responder if he or she met both of the following criteria:

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

To be eligible to be a responder, a patient must have had a minimum of 60 days of diary entries over the 12-week interval (70% diary entry completion). Any patient with fewer than the minimum days of diary entries was considered a non-responder. Descriptions of individual patient reported outcome efficacy assessment measures from the daily diary are provided in **Table 12** below.

Reviewer Comments: The Primary endpoint was agreed upon in meetings with the FDA and is consistent with the recommendations in the FDA Guidance for Industry Irritable Bowel Syndrome – Clinical Evaluation of Drugs for Treatment.

Secondary Efficacy Endpoints
IBS-3001 and -3002
Secondary endpoints included the following:

- Composite responders (defined above) over each of the following intervals to assess durability of treatment: Weeks 1–4, Weeks 5-8, Weeks 9-12, Weeks 1-26.
- Pain responders over the intervals from Weeks 1–4, Weeks 5-8, Weeks 9-12, Weeks 1-12, and Weeks 1-26.
- Stool consistency responders over the intervals from Weeks 1–4, Weeks 5-8, Weeks 9-12, Weeks 1-12, and Weeks 1-26.
- IBS global symptom responders over the intervals from Weeks 1–4, Weeks 5-8, Weeks 9-12, Weeks 1-12, and Weeks 1-26.
- IBS-QoL responders
- IBS adequate relief responders over the intervals from Weeks 1-12 and Weeks 1-26.

A patient must have had a minimum of 20 days of diary entries over any 4-week interval, 60 days over a 12-week interval, and 110 days over a 26-week interval to be a responder. Responder definitions are provided in **Table 11**.

Table 11: Responder definitions:

Responder Term	Definition
Pain Responder	patients who met the daily pain response criteria (described above) for at least 50% of days with diary entries during each interval over the 12-week interval, 26-week interval, and each 4-week interval
Stool consistency responder	patients who met the daily stool consistency response criteria (described above) for at least 50% of days with diary entries during each interval over the 12-week interval, 26-week interval, and each 4-week interval
IBS-d global symptom responder	patients who met the daily IBS-d global symptom response criteria (IBS-d global symptom score of 0 [none] or 1 [mild]; or a daily symptom score improved by ≥ 2.0 compared to the baseline average) for at least 50% of days with diary entries during each interval over the 12-week interval, 26-week interval, and each 4-week interval
IBS-QoL responder	patients who achieved at least a 14-point improvement in IBS-QoL total score from baseline to applicable visit.
IBS-AR responder	patients with a weekly response of "yes" to adequate relief of their IBS symptoms for at least 50% of the total weeks during the 12-week and 26-week intervals. A patient must have had a positive response for ≥ 6 weeks for the 12-week interval and ≥ 13 weeks for the 26-week interval.

Source: Summarized from Applicant Clinical Study Protocol IBS-3001

Other secondary endpoints included:

- Discomfort: changes from baseline in daily abdominal discomfort scores
- Bloating: changes from baseline in daily abdominal bloating scores
- Frequency: number of bowel movements per day
- Incontinence: number of bowel incontinence episodes per day and number of
- incontinence-free days
- Urgency: number of urgency episodes per day
- IBS-QoL: total score and scores compared to baseline

Table 12: Patient Reported Efficacy Assessment Measures

Score	Definition
Worst abdominal pain score	Worst pain in the past 24 hours, recorded on a 0 to 10 scale, where 0 corresponds to no pain and 10 corresponds to worst imaginable pain
Abdominal discomfort score	Abdominal discomfort in the past 24 hours recorded on a 0 to 10 scale, where 0 corresponds to no discomfort and 10 corresponds to worst imaginable discomfort
Abdominal bloating score	Bloating in the past 24 hours recorded on a 0 to 10 scale, where 0 corresponds to no bloating and 10 corresponds to worst imaginable bloating
Bristol stool score	BSS most representative of the past 24 hours based on a 1 to 7 scale where 1 corresponds to hard stool and 7 corresponds to watery diarrhea
IBS-d global symptom score	Overall IBS-d global symptoms in the past 24 hours on a 0 to 4 scale where: • 0 corresponds to no symptoms • 1 corresponds to mild symptoms • 2 corresponds to moderate symptoms • 3 corresponds to severe symptoms • 4 corresponds to very severe symptoms
Frequency, urgency, and incontinence	The number of bowel movements, number of incontinence episodes, and number of urgency episodes over the past 24 hours.
IBS-adequate relief (IBS-AR)	IBS-AR score is a dichotomous single item (yes/no) used to assess adequate relief of IBS symptoms over the past week.

Source: Summarized from Applicant Clinical Study Protocol IBS-3001

5.3.8 Statistical Information

IBS-3001 and -3002

The reader is referred to Dr. Yeh-Fong Chen's statistical review for detailed information of the Applicant's statistical analysis.

The Applicant calculated a sample size of approximately 375 patients per treatment group. This sample size yields approximately 90% power for a 2-sided CMH test at an α level of 0.025, assuming a placebo response for the primary efficacy endpoint of 14% and a 10% treatment effect over placebo for any active group. The primary analysis set for all efficacy analyses was the Intention-to-Treat population, defined as all patients randomly assigned to treatment.

A Bonferroni p-value adjustment will be used to control for multiple tests of the primary endpoint (2 active treatment doses). No adjustment for multiple comparisons will be made for secondary analyses.

Missing Data Handling: Based on IVR compliance data from Phase 2 trials, the Applicant anticipated ~15% missed diary calls for patients who continue in Phase 3

studies and thus, allowed for flexibility with regard to missed daily diary calls. If no diary entry was made for a given day then it was considered a missing day. A given patient is eligible for evaluation as a responder if he or she has at least 70% of days within a given period with an IVR diary call logged. Patients not meeting this criterion will be treated as non-responders. If worst abdominal pain was entered for a given day, but the BSS was missing, the patient would be considered a responder for that day if pain criteria was met (i.e., because no bowel movement was reported on that day). Otherwise a patient reporting no BMs on a given day in absence of a pain response would be a non-responder for that day.

5.3.9 Protocol Amendments

IBS-3001 and -3002
Study IBS-3001 and IBS-2003 were originally dated 04March2012 and had 4 identical protocol amendments between 04June2012 and 04December2013. The amendments are summarized below:

Amendment 1 (04June2012): the purpose of this amendment was to incorporate feedback from the US and EU regulatory agencies (primarily adding the 26 week assessments and endpoints for EMA), to clarify eligibility criteria, and to clarify the timing of assessments to be performed. Specific revisions included:

- Changed duration of electronic diary collection and notifications for constipation, excess rescue medication usage, and patients' compliance from 12 weeks to 26 weeks
- Added daily assessment of abdominal discomfort to electronic diary collection
- Added exclusion criteria for lactose intolerance and gastrointestinal infection and clarified the definition of alcohol abuse and binge drinking
- Clarified the use of rescue medications (loperamide extended from 12 to 26 weeks), prohibited medications (added tramadol), and concomitant medications (extended prohibition of concomitant medications that could interfere with study from 12 to 26 weeks)

Amendment 2 (24August2012): The purpose of this Amendment was to clarify eligibility criteria and the reporting period for pregnancies. Specific revisions included:

- Added microscopic colitis as an example of an excluded inflammatory bowel disease
- Changed the pregnancy reporting requirement to the time of the first dose of study drug, to be consistent with the inclusion criteria

Amendment 3 (30October2012): The purpose of this Amendment was to add guidance in the event of elevated liver enzymes (e.g., timing of repeat labs and withdrawal criteria) and clarify eligibility criteria and electronic diary notifications. Specifically, this Amendment clarified that the electronic diary does not send a notification of eligibility to

the sites (related to diary compliance, loperamide rescue medication uses, etc.), rather the Investigator must re-verify that the patient meets all inclusion/exclusion criteria at the time of randomization.

Amendment 4 (04December2013): The purpose of this Amendment was to incorporate recommendations from the EMA regarding the EMA primary endpoint and timing for data extraction.

6 Review of Efficacy

Efficacy Summary

Clinical trials IBS-3001 and IBS-3002 provided statistically persuasive evidence to support that eluxadoline 100mg BID and 75mg BID are effective for the treatment of diarrhea and abdominal pain in adults with diarrhea predominant irritable bowel syndrome (IBS-d). Two phase 3 clinical trials (IBS-3001 and IBS-3002) were conducted to support this efficacy claim. The design and objectives of the two studies were identical, and the primary objective was to demonstrate that eluxadoline 100 mg twice daily and eluxadoline 75 mg twice daily are superior to placebo in reducing abdominal pain and improving stool consistency during a 12-week double-blind treatment period. The study cohorts consisted of adult patients with IBS-d (by Rome III criteria) who met screening and baseline criteria for pain, stool consistency, and IBS-d global symptoms (see Section 5.1 Protocol Summary for specific inclusion criteria).

The pre-specified primary endpoint in both studies was the proportion of composite responders over the initial 12 week double-blind period. A patient was a composite responder if he or she met the daily response criteria for at least 50% of the days with diary entries during Weeks 1 – 12. A patient was a daily responder if he or she met both of the following criteria:

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

Both Studies also included efficacy assessments over the first 26 weeks of the study. IBS-3001 continued through Week 52 for controlled, double-blind safety data, whereas IBS-3002 included a 4-week single blind withdrawal period to assess for rebound effects. See Sections 5.3.1 and 5.3.2 for a discussion of the study protocols for Study IBS-3001 and IBS-3002, respectively. The design and conduct of both trials was

identical through Week 26, including primary and secondary endpoints. Efficacy data is thus shown throughout Section 6 with results from both phase 3 studies side by side.

In Study IBS-3001, the proportion of composite responders was significantly higher in patients receiving eluxadoline 100mg BID compared to placebo (25.1% vs 17.1%, p = 0.004) over Weeks 1 - 12. The proportion of composite responders was also significantly higher in patients receiving eluxadoline 75mg BID compared to placebo (23.9% vs 17.1%, p = 0.014). Similarly, in Study IBS-3002, the proportion of composite responders was significantly higher in patients receiving eluxadoline 100mg BID and 75mg compared to placebo (29.6% 100mg and 28.9% 75mg vs 16.2% placebo, p<0.001).

6.1 Indication

The Applicant is proposing the eluxadoline receive an indication for the treatment of adults with diarrhea predominant irritable bowel syndrome (IBS-d).

6.1.1 Methods

Two phase 3 clinical trials (IBS-3001 and IBS-3002) were conducted to support the efficacy claim for eluxadoline for the treatment of diarrhea and abdominal pain in men and women with diarrhea predominant irritable bowel syndrome (IBS-d). IBS-3001 and IBS-3002 were multicenter, multinational, randomized, double-blind, placebo-controlled, phase 3 studies which included 2425 adult patients with IBS-d in the intention-to-treat population for efficacy analyses. The design and conduct of both trials was identical through Week 26, including primary and secondary endpoints. Primary efficacy evaluation was based on the patient's daily self-assessment (collected using IVRS) of daily worst abdominal pain and stool consistency.

The definition of study populations included in the efficacy and safety analyses for IBS-3001 and IBS-3002 are described in **Table 13**. The primary set for all efficacy analyses was the ITT analysis set.

Table 13: Definition of Analysis Sets for IBS-3001 and IBS-3002

Analysis Set	Definition
Enrolled	All patients randomized or who received at least 1 dose of study drug. The enrolled set was used for presentation of demographic and baseline characteristic data.
Intention-to-treat (ITT)	All patients randomly assigned to treatment. The ITT is the primary set for all efficacy analyses.
Modified intention-to-treat (MITT)	All patients randomly assigned to treatment who received at least 1 dose of study drug and who had Baseline and at least one post-randomization diary entry.
Safety	All patients enrolled who received at least one dose of study drug. Any analysis based on the safety analysis set will be based on the treatment actually received.

Source: Reviewer's table, summarized from Applicant's Clinical Study Reports for IBS-3001 and IBS-3002

6.1.2 Demographics

The study population for both IBS-3001 and IBS-3002 consisted of adults with IBS-d, diagnosed by Rome III criteria (See Section 5.3 for full inclusion criteria). **Table 14** presents select baseline demographic data for the two phase 3 trials.

Table 14: Demographic Characteristics (Enrolled Set)

Variable	IBS-3001			IBS-3002		
	Eluxadoline 75 mg BID N = 429	Eluxadoline 100 mg BID N = 426	Placebo BID N = 427	Eluxadoline 75 mg BID N = 381	Eluxadoline 100 mg BID N = 383	Placebo BID N = 382
Age (years)						
Mean (SD)	44.5 (13.18)	44.4 (13.91)	45.8 (14.10)	45.0 (13.17)	45.7 (13.31)	47.1 (13.82)
Min, Max	18, 80	18, 79	18, 79	18, 77	19, 75	18, 77
Age group, n (%)						
18 – 40	173 (40.3)	166 (39.0)	159 (37.2)	139 (36.5)	146 (38.1)	133 (34.8)
41 – 64	227 (52.9)	225 (52.8)	217 (50.8)	206 (54.1)	198 (51.7)	198 (51.8)
≥ 65	29 (6.8)	35 (8.2)	51 (11.9)	36 (9.4)	39 (10.2)	51 (13.4)
Gender, n (%)						
Male	151 (35.2)	143 (33.6)	150 (35.1)	120 (31.5)	126 (32.9)	132 (34.6)
Female	278 (64.8)	286 (66.4)	277 (64.9)	261 (68.5)	257 (67.1)	250 (65.4)
Country, n (%)						
USA	405 (94.4)	404 (94.8)	405 (94.8)	366 (96.1)	366 (95.6)	366 (95.8)
Canada	9 (2.1)	8 (1.9)	8 (1.9)	10 (2.6)	12 (3.1)	10 (2.6)
United Kingdom	15 (3.5)	14 (3.3)	14 (3.3)	5 (1.3)	5 (1.3)	6 (1.6)
Race, n (%)						
White	374 (87.2)	368 (86.4)	370 (86.7)	327 (85.8)	318 (83.0)	329 (86.1)
Black	46 (10.7)	48 (11.3)	46 (10.8)	46 (12.1)	51 (13.3)	43 (11.3)
Asian	3 (0.7)	3 (0.7)	4 (0.9)	2 (0.5)	7 (1.8)	6 (1.6)
AmIndian or Alaska Native	1 (0.2)	2 (0.5)	1 (0.2)	3 (0.8)	3 (0.8)	1 (0.3)
Native Hawaiian/ Pacific Islander	0	1 (0.2)	0	0	1 (0.3)	2 (0.5)
Other	5 (1.2)	4 (0.9)	6 (1.4)	3 (0.8)	3 (0.8)	1 (0.3)
Ethnicity, n (%)						
Hispanic or Latino	119 (27..7)	117 (27.5)	125 (29.3)	98 (25.7)	99 (25.8)	101 (26.4)
Non-Hispanic or Latino	310 (72.3)	309 (72.5)	302 (70.7)	283 (74.3)	284 (74.2)	281 (73.6)
BMI (kg/m^2)						
N	428	424	425	381	383	382
Mean (SD)	30.70 (7.42)	31.22 (7.86)	30.63 (7.25)	30.79 (8.17)	30.45 (7.74)	29.79 (6.87)
Min, Max	17.8, 54.6	16.7, 60.9	16.9, 72.3	15.5, 65.8	16.0, 63.5	14.8, 69.6

Source: Modified from Table 11-2 from CSR IBS-3001 and demographics dataset for IBS-3001, Table 11.2 from CSR IBS-3002 and demographics dataset from IBS-3002

Reviewer Comments: The majority of patients were white and female in both Phase 3 studies, and approximately 95% of patients in both studies were from the US. Demographics were generally similar between treatment groups in both studies. The proportion of patients ≥ 65 was slightly higher in the placebo group in both studies, compared to the 75mg and 100mg eluxadoline groups, but this reviewer does not believe this should have a substantial impact on results. This reviewer believes the baseline demographic characteristics of patients in both studies was sufficiently similar and that the eluxadoline and placebo arms were generally well matched within both phase 3 trials, with regard to gender, race, and age. Furthermore, the baseline demographics are similar to the demographics of IBS patients in the US, where the majority of IBS patients are white and female, and the prevalence of IBS declines after age 60.

Most patients had IBS symptoms that tended to be persistent over time (79.6% in IBS-3001 and 78.3% in IBS-3002. Approximately 36% of patients in IBS-3001 used loperamide in the year prior to enrollment for IBS symptoms, and this was slightly higher percentage in the eluxadoline treatment arms compared to placebo (36.1% 75mg BID, 39.4% 100mg BID vs 33.5% placebo). Similarly, 35.6% of patients in IBS-3002 used loperamide in the year prior to enrollment. The majority of patients in both studies who used loperamide did not experience adequate control of their IBS symptoms from their treatment (64.8% in IBS-3001 and 58.1% in IBS-3002). A comparison by treatment arms of select baseline IBS characteristics during the week prior to dosing is presented in **Table 15** below, excluding cases for which information is not known (i.e., due to electronic diary noncompliance).

Table 15: Select Baseline IBS characteristics for IBS-3001 and IBS-3002 (Randomized Patients)

Variable	IBS-3001			IBS-3002		
	Eluxadoline 75 mg BID N = 428	Eluxadoline 100 mg BID N = 426	Placebo BID N = 427	Eluxadoline 75 mg BID N = 381	Eluxadoline 100 mg BID N = 383	Placebo BID N = 382
Worst Abdominal pain						
Mean (SD)	6.13 (1.546)	6.19 (1.507)	6.24 (1.565)	6.00 (1.503)	5.95 (1.511)	6.04 (1.492)
Median	6.0	6.0	6.2	5.9	5.9	6.0
Min, Max	3.1, 10.0	3.1, 10.0	3.1, 10.0	3.1, 10.0	3.1, 10.0	3.1, 10.0
Stool consistency (BSS)						
Mean (SD)	6.25 (0.414)	6.28 (0.422)	6.26 (0.410)	6.24 (0.390)	6.20 (0.406)	6.22 (0.413)
Median	6.10	6.20	6.20	6.20	6.10	6.10
Min, Max	5.5, 7.0	5.5, 7.0	5.4, 7.0	5.5, 7.0	5.5, 7.0	5.5, 7.0
Bowel movement frequency						
Mean (SD)	4.85 (2.699)	4.96 (2.999)	5.00 (2.736)	4.71 (2.318)	4.94 (4.164)	4.69 (2.247)
Median	4.40	4.40	4.60	4.20	4.40	4.30
Min, Max	1.0, 29.4	1.0, 45.3	1.0, 33.6	1.3, 17.0	1.4, 75.0	0.9, 14.4
IBS-d global symptom score						
Mean (SD)	2.80 (0.548)	2.87 (0.538)	2.88 (0.547)	2.76 (0.536)	2.79 (0.512)	2.81 (0.540)
Median	2.90	3.00	2.90	2.80	2.90	2.80
Min, Max	2.0, 4.0	2.0, 4.0	2.0, 4.0	2.0, 4.0	2.0, 4.0	2.0, 4.0

Source: Table 11-3 from CSR IBS-3001 and Table 11-3 from CSR IBS-3002

Reviewer Comments: The baseline IBS disease characteristics averaged from the 7 days prior to Day 1 were comparable across treatment groups and between studies. Patients enrolled in IBS-3001 had an average worst abdominal pain score of 6.19, compared to 6.00 for patients enrolled in IBS-3002. The mean daily BSS score was 6.27 for patients enrolled in IBS-3001, compared to 6.22 for those in IBS-3002. In addition to the disease characteristics shown in Table 15, baseline characteristics related to daily incontinence, urgency episodes and incontinence episodes were similar across treatment groups. Patients experienced an average of 3.5 urgency episodes per day over the 7 days prior to Day 1 dosing (3.54 in IBS-3001 and 3.47 in IBS-3002), and incontinence episodes were uncommon across all groups (<1 median). This reviewer feels the baseline disease characteristics reflected patients with significant symptoms of IBS-d and were comparable across treatment groups and studies.

6.1.3 Subject Disposition

In **IBS-3001**, a total of 3825 patients were prescreened and 2832 were found eligible to enter a 2-week screening period, during which time they were to complete a daily electronic diary related to their IBS-d symptoms, bowel functioning, and loperamide use.

Patients were required to meet prespecified IVRS criteria during the screening period, described in Section 5.3.1, in order to be enrolled in the study. The most common reasons for screening failure were diary non-compliance, failure to meet BSS criteria, and other. Overall 1282 patients were enrolled in IBS-3001. In **IBS-3002**, a total of 3356 patients were prescreened, 2521 entered the screening period, and 1146 patients were enrolled. Similar reasons (diary non-compliance, failure to meet BSS criteria) were given for screening failure in IBS-3002 as IBS-3001.

One patient in study **IBS-3001** (057/0001) received eluxadoline 75mg BID but was never randomized, thus the randomized set for this study includes one fewer patient than the enrolled set (1281 vs 1282). In addition, **both studies IBS-3001 and IBS-3002** had a single patient who was randomized twice (001/0027 and 176/0005 for IBS-3002; 502/0004 and 545/0001 for IBS-3002). In both instances, only data from the first randomization was included in the ITT Analysis Set. The ITT set used for all primary and secondary analyses includes 1280 patients in Study **IBS-3001** and 1145 patients in **IBS-3002**. The datasets for IBS-3001 and IBS-3002 are summarized in **Table 16**.

Table 16: Analysis Sets (Enrolled Set)

Analysis Set	IBS-3001				IBS-3002			
	Eluxadoline 75 mg BID	Eluxadoline 100 mg BID	Placebo BID	Total	Eluxadoline 75 mg BID	Eluxadoline 100 mg BID	Placebo BID	Total
Enrolled Set	429[a]	426	427	1282	381	383	382	1146
Randomized Set	428[b]	426	427	1281	381	383	382	1146
ITT Analysis Set	427	426	427	1280	381	382	382	1145
MITT Analysis Set	422	421	424	1267	376	376	379	1131
Safety Analysis Set	428	479[c]	427	1276	379	380	381	1137

Source: Table 11-1 of Clinical Study Report IBS-3001 and Table 11-1 of Clinical Study Report IBS-3002
[a] The enrolled set for IBS-3001 includes 1 patient who received eluxadoline 75 mg BID due to a site dispensation error, but was never randomized (057/0001)
[b] The randomized set for IBS-3001 includes a single individual who was unintentionally randomized twice in the study and assigned 2 patient IDs (001/0027 and 176/0005) due to the patient trying to participate at more than one study center at once. 176/0005 was excluded from the ITT analysis set.
[c] The safety analysis set in the 100-mg eluxadoline group for IBS-3001 includes 53 patients randomized to the 75mg group who received eluxadoline 100mg in error for 1 to 131 days due to a systemic error in the IVRS system.

Reviewer comment: The safety analysis set for Study IBS-3001 includes 53 patients in both the 75 and 100mg treatment arms in an attempt to account for a systemic error in the IVRS system resulting in treatment misallocation (from 75mg to 100mg) for 1 to 131 days in 53 patients. While this reviewer agrees that it is reasonable to record AEs according to the actual treatment received at the time of the AE, counting patients in both treatment arms may lower incidence rates for AEs, as the denominator is artificially high. Given the relatively small number of misallocations, in comparison to the treatment arms, and given that patients remained on investigational therapy, only at a slightly

higher dose, it is unlikely that this will impact the safety results. This is discussed further in Section 7: Review of Safety.

In **IBS-3001**, 40.1% (172 patients) in the 75mg arm, 60.3% (168 patients) in the 100mg arm, and 37.0% (158 patients) in the placebo group discontinued prematurely from the trial. Of note, 79% of patients attended through the Week 12 visit when data collection associated with the primary efficacy endpoint was complete (primary efficacy endpoint was the proportion of composite responders over the initial 12 week double-blind period). The most common reason for discontinuation was voluntary withdrawal by the patient (21.0% total patients), followed by discontinuation due to adverse events, which occurred more frequently in the eluxadoline arms than in the placebo arm (8.6% and 10.6% vs 4.0% placebo).

In **IBS-3002**, 65.6% (250 patients) in the 75mg arm, 68.9% (264 patients) in the 100mg arm, and 71.5% (273 patients) in the placebo group discontinued prematurely from the trial. A similar proportion of patients continued through the Week 12 visit as was observed in IBS-3001 (79.3% in IBS-3002 vs 79.0% in IBS-3001). Reasons for withdrawal were similar to IBS-3001 and included: voluntary withdrawal by the patient (18.3% total patients) and discontinuation due to adverse events, which occurred more frequently in the eluxadoline arms than in the placebo arm (8.7% and 7.6% vs 5.0% placebo).

Study disposition for IBS-3001 and IBS-3002, including reasons for discontinuation, are presented in **Table 17** below.

Table 17: Disposition (Enrolled Set)

Disposition, n(%)	IBS-3001				IBS-3002			
	Eluxadoline 75 mg BID N = 429	Eluxadoline 100 mg BID N = 426	Placebo BID N = 427	Total N = 1282[a]	Eluxadoline 75 mg BID N = 381	Eluxadoline 100 mg BID N = 383	Placebo BID N = 382	Total N = 1146
Randomized,	428 (99.8)	426 (100.0)	427 (100.0)	1281 (99.9)	381 (100.0)	383 (100.0)	382 (100.0)	1146 (100.0)
Attended Week 12 visit	341 (79.5)	330 (77.5)	342 (80.1)	1013 (79.0)	296 (77.7)	301 (78.6)	312 (81.7)	909 (79.3)
Attended Week 26 visit	289 (67.4)	291 (68.3)	290 (67.9)	870 (67.9)	259 (68.0)	271 (70.8)	278 (72.8)	808 (70.5)
Completed study	257 (59.9)	257 (60.3)	269 (63.0)	783 (61.1)	250 (65.6)	264 (68.9)	273 (71.5)	787 (68.7)
Discontinued study	172 (40.1)	168 (39.4)	158 (37.0)	498 (38.8)	131 (34.4)	119 (31.1)	109 (28.5)	359 (31.3)
IVRS/IWRS misallocation	53 (12.4)	0	0	53 (4.1)	12 (3.1)	13 (3.4)	0	25 (2.2)
Primary Reason for Discontinuation, n (%)								
Voluntarily withdrew	94 (21.9)	79 (18.5)	96 (22.5)	269 (21.0)	70 (18.4)	66 (17.2)	74 (19.4)	210 (18.3)
Adverse event or SAE[b]	37 (8.6)	45 (10.6)	17 (4.0)	99 (7.7)	33 (8.7)	29 (7.6)	19 (5.0)	79 (6.9)
Lost to follow-up	25 (5.8)	23 (5.4)	16 (3.7)	64 (5.0)	11 (2.9)	5 (1.3)	6 (1.6)	22 (1.9)
Physician decision; other[c]	10 (2.3)	14 (3.3)	15 (3.5)	41 (3.2)	9 (2.4)	8 (2.1)	7 (1.8)	25 (2.2)
Physician decision; lack of efficacy[d]	2 (0.5)	3 (0.7)	7 (1.6)	12 (0.9)	1 (0.3)	6 (1.6)	3 (0.8)	10 (0.9)
Protocol violation[e]	3 (0.7)	4 (0.9)	4 (0.9)	11 (0.9)	0	2 (0.5)	0	2. (0.2)
Sponsor decision[f]	1 (0.2)	0	3 (0.7)	4 (0.3)	7 (1.8)	3 (1.3)	1	12 (1.0)

Source: Modified from Table 14.1.1 from Clinical Study Report IBS-3001 and 16.2.1 Disposition Enrolled Set Data Listings and Applicant Response to Information Request dated 22September2014.

[a] The total number of patients enrolled includes patients who were randomized or who received at least one dose of study drug, 1 patient (057/0001) received study drug but was never randomized

[b] Two (2) patients were withdrawn for AEs (abnormal LFTs in 75mg arm, abdominal pain in placebo arm) from IBS-3001 but categorized by the Applicant as discontinuing for "other". These were recategorized as AE.

[c] Reasons for discontinuation due to Physician decision (other) were patient noncompliance, patient overwhelmed with diary requirements, incarceration, surgery, subject dishonesty, transportation issues, patient needing restricted medications, and pregnancy.

[d] One (1) patient in IBS-3002 was withdrawn due to lack of efficacy but was categorized by the Applicant as discontinuing for "other. This was recategorized as lack of efficacy.

[e] "Protocol violation" leading to discontinuation included scheduling error, prohibited medication, entry criteria error (h/o pancreatitis, lactose intolerance, no recent colonoscopy), attempting to enroll at different sites

[f] Discontinuations due to Sponsor decision included a site closing impacting 1 patient from the 75mg group and 2 patients from the placebo group and 1 patient in the placebo group discovered to have biliary dyskinesia based on an ER visit for abdominal pain. In study IBS-3002, discontinuation due to Sponsor decision was primarily due to misallocation of kits due to IVRS error

Reviewer Comment: There was a high proportion of patients who discontinued prematurely from the trial in all treatment groups. The discontinuation rate at 12 weeks (time for primary endpoint analysis) was approximately 79% in both IBS-3001 and IBS-3002, with a slightly higher discontinuation rate in the placebo arm, compared to the eluxadoline arms. This is similar to alosetron which had a 22% discontinuation rate during a 12-week treatment phase. This reviewer notes poor coding quality in the disposition domain of the Applicant's datasets for IBS-3001 and IBS-3002. Terms were coded to "other" and "voluntarily withdrew" which could have more appropriately been mapped to other terms, however the proportion was similar across treatment groups and should not impact results. The proportion of patients who withdrew due to lack of efficacy was small in both studies; however, the most common reason for discontinuation was voluntary withdrawal which does not provide a clear reason for discontinuation. Rates of discontinuation due to voluntary withdrawal were similar across treatment groups, however, and thus not likely to impact efficacy results. Discontinuation due to adverse events was higher in the eluxadoline arms, which is not unexpected. The overall discontinuation rates were slightly higher in eluxadoline groups, however, in this reviewer's assessment there were no clinically important differences in subject disposition between the two arms of either of the studies.

Protocol violations/Deviations:
Protocol violations in IBS-3001 and IBS-3002 are summarized in **Table 18** below. Most protocol violations did not result in patients being excluded from the primary efficacy and safety analyses, except for 11 patients in IBS-3001 and 2 patients in IBS-3002, as noted in **Table 17** above.

Table 18: Protocol Violations[a], Enrolled Set, IBS-3001 and IBS-3002

Type of Protocol Violation	Eluxadoline 75 mg BID N = 428	Eluxadoline 100 mg BID N = 426	Placebo BID N =427	Total N =1282	Eluxadoline 75 mg BID N = 381	Eluxadoline 100 mg BID N = 383	Placebo BID N =382	Total N =1146
Patients with protocol violations n (%)	56 (13.1)	63 (14.8)	56 (13.1)	175 (13.7)	30 (7.9)	37 (9.7)	33 (8.6)	100 (8.7)
Informed consent issues	7 (1.6)	7 (1.6)	3 (0.7)	17 (1.3)	2 (0.5)	2 (0.5)	4 (1.0)	8 (0.7)
Inclusion /exclusion issues	37 (8.6)	39 (9.2)	45 (10.5)	121 (9.4)	23 (6.0)	25 (6.5)	17 (4.5)	65 (5.7)
Excluded medication taken	13 (3.0)	24 (5.6)	12 (2.8)	49 (3.8)	8 (2.1)	10 (2.6)	12 (3.1)	30 (2.6)

Source: Applicant response to Information Request dated 09/22/2014.
[a] Includes all patients with protocol violations categorized as informed consent issues, inclusion/exclusion issues, or excluded medication taken.

In addition, a number of treatment misallocations occurred in both studies, both as a result of systematic errors in the IVRS and drug dispensation errors at individual sites. These additional protocol violations were:

- IBS-3001: Fifty-eight (58) patients took the wrong drug due to a systematic error in the IVR/IWR system. All 58 patients were randomized to the 75 mg eluxadoline group and were dispensed the 100mg treatment kits at the Week 18 visit. Five (5) of these patients returned their entire misallocated kit and were dispensed the correct kit, and the remaining 53 took the wrong treatment for 1 to 131 days.
- IBS-3001: Five (5) patients received the wrong drug due to a site kit misallocation (errors due to site personnel) resulting in exposure to incorrect treatment for 28 – 69 days. This is shown in **Table 19** below.
- IBS-3002: Twenty-five (25) patients continued to take active study drug during the 4-week single-blind withdrawal period due to a systematic error in the IVR/IWR system. This resulted in 12 patients taking 75mg eluxadoline instead of placebo and 13 patients taking 100mg eluxadoline instead of placebo.
- IBS-3002: Three (3) patients received the wrong drug due to a site kit misallocation (errors due to site personnel) resulting in exposure to incorrect treatment for 28 – 69 days. This is shown in **Table 19** below.

Table 19: Site Kit Misallocations in Study IBS-3001 and IBS-3002

Randomized Treatment Arm	Patient ID	Visit	Incorrect Dose Received	Exposure to Incorrect Treatment (Days)
IBS-3001				
100 mg	008/0029	Week 12	Placebo	37
Placebo	008/0024	Week 18	100 mg	48
	025/0010	Week 4	75 mg	28
	063/0001	Week 26	100 mg	66
	171/0001	Week 26	75 mg	69
IBS-3002				
100 mg	771/0001	Week 8	75 mg	34
Placebo	564/0006	Week 18	100 mg	56
	642/003	Day 1	75 mg	28

Source: Applicant Clinical Study Reports IBS-3001 and IBS-3002 Data Listing 16.2.3.3

Finally, a site audit concluded that some staff members at site 363 were making patient diary entries into the system on their patient's behalf to assist with diary compliance. This would require the site staff to know the patient's daily symptom scores which they should have remained blinded to, per the protocol. Site 363 enrolled 8 patients into study IBS-3001.

Reviewer Comments: This reviewer believes that protocol violations were comparable across treatment arms and unlikely to impact the efficacy evaluation. This medical officer reviewed the violations of entry criteria for the ITT population. The majority of the violations of eligibility criteria would have no impact on the efficacy evaluation (e.g., h/o alcohol abuse, allergy to opioids, pregnant or breastfeeding, patients who are not postmenopausal, etc.). This reviewer categorized only 19 violations of entry criteria in Study IBS-3001 and 12 violations of entry criteria in Study IBS-3002 from the ITT population as possibly impacting that individual's efficacy response (e.g., use of 5HT3 antagonists within 14 day or current use of rifaximin). These were equally distributed among treatment arms, however, and should not impact results.

The treatment misallocations which occurred in studies IBS-3001 and IBS-3002 as a result of systematic errors in the IVRS occurred at Week 18 and Week 26, respectively. These results will not impact the primary or key secondary analyses, as these endpoints were assessed from Weeks 1 – 12. Site kit misallocations due to drug dispensation errors at individual sites occurred in a small number of patients (5 in IBS-3001 and 3 in IBS-3002) and were thus unlikely to impact results. Furthermore, the majority of the patients incorrectly received investigational drug when they were assigned to placebo which would favor placebo in the efficacy evaluation. This reviewer agrees with the Applicant's approach to analyzing these patients according to the randomization assignment, regardless of treatment received.

The diary entry by site staff at site 363 is concerning, in that is brings into question the trial conduct at that site, however, there were only 8 patients enrolled to IBS-3001 from that site, so the results from this site should not impact overall efficacy results.

6.1.4 Analysis of Primary Endpoint(s)

As previously described, the primary endpoint for IBS-3001 and -3002 was the proportion of composite responders over the initial 12 week double-blind period. A patient was a composite responder if he or she met the daily response criteria for at least 50% of the days with diary entries during Weeks 1 – 12. A patient was a daily responder for a given day if he or she met the criteria for both a daily pain response and a daily stool consistency response.

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

For the EMA, the primary endpoint was the proportion of composite responders over the interval from Weeks 1 – 26. Both are shown in **Table 20** below for the 75 and 100 mg treatment groups.

Table 20: Proportion of Composite Responders

Treatment	Number (%)		P value[a]
	Responder	Non-responder	
Study IBS-3001			
Weeks 1 – 12			
Eluxadoline 75 mg BID (N = 427)	102 (23.9)	325 (76.1)	0.014
Eluxadoline 100 mg BID (426)	107 (25.1)	319 (74.9)	0.004
Placebo BID (N = 427)	73 (17.1)	354 (82.9)	---
Weeks 1 – 26			
Eluxadoline 75 mg BID (N = 427)	100 (23.4)	327 (76.6)	0.112
Eluxadoline 100 mg BID (426)	125 (29.3)	301 (70.7)	< 0 .001
Placebo BID (N = 427)	81 (19.0)	346 (81.0)	---
Study IBS-3002			
Weeks 1 – 12			
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			
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)	---

[a]P value is based on Chi-square test statistic. Each active treatment group versus placebo comparison was assessed at 0.025 significance level to preserve the family-wise error rate using the Bonferroni adjustment.
Source: Table 14.2.2.1.1 and 14.2.2.1.3 from Applicant Complete Study reports IBS-3001 and IBS-3002

Reviewer Comment: 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.

*In Study **IBS-3001**, 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 difference was even greater when looking over Weeks 1 – 26 (29.3% vs 19.0%, p < 0.001) for the 100mg BID group, though the 75mg group did not reach statistical significance over 26 weeks of treatment.*

*In Study **IBS-3002,** a significantly higher proportion of patients in both eluxadoline arms were composite responders compared to placebo when looking through Week 12*

(28.9% 75mg, 29.6% 100mg, vs 16.2% placebo) and through Week 26 (30.4% 75mg, 32.7% 100mg, vs 20.2%).
The response rates appeared greater when assessing over the longer treatment period (i.e. 26 weeks) in both studies. Previous registration trials in IBS-D (i.e., alosetron) assessed "adequate relief of IBS pain and discomfort". The currently designed analysis is, in this reviewers opinion, more rigorous, but still shows similar improvement in symptoms over placebo.

Interval Analyses of Composite Responders

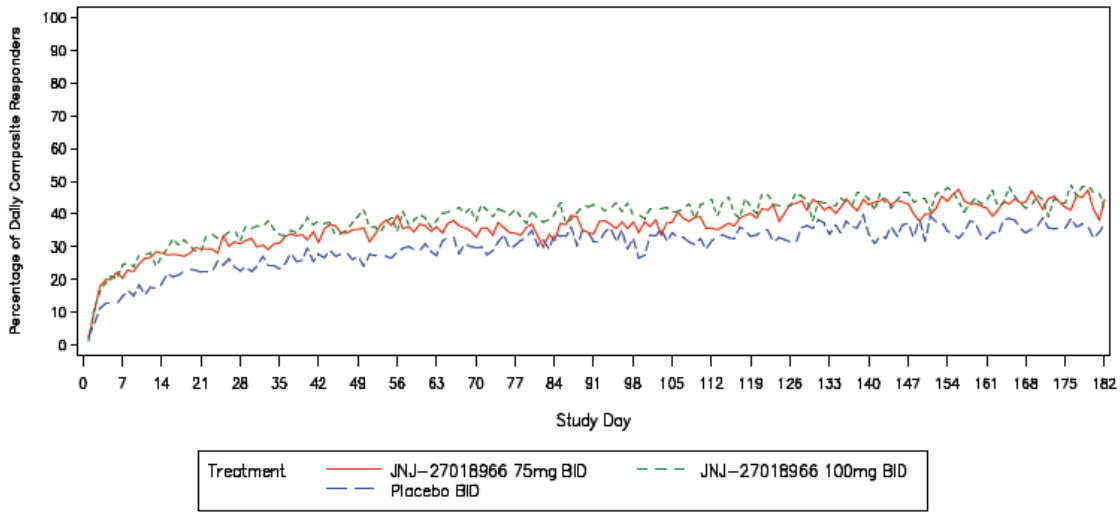
In order to assess the durability of response over the course of treatment through Week 26, the Applicant analyzed the proportion of composite responders over 4-week intervals and found that the proportion of composite responders was higher in both eluxadoline treatment groups compared to placebo for each of the 4-week intervals for both IBS-3001 and IBS-3002 (Weeks 1 – 4, 5 – 8, 9 – 12, 13 – 16, 17 – 20, 21 – 24, 25 – 28). In study **IBS-3001**, these differences were statistically significant ($p < 0.05$) for most intervals in the 75mg group and for all intervals for the 100mg group. In **IBS-3002**, these differences were statistically significant ($P < 0.05$) for all of the intervals for both eluxadoline treatment groups. **Table 21** below shows the CMH Analysis of Composite responders by interval, and **Figure 3** and **Figure 4** below present line plots of percentage of daily composite responders from Day 1 through Day 182 (Week 26) for each treatment group from the respective studies. The daily composite response rates were consistently higher for both eluxadoline groups compared with placebo in Study IBS-3001 and IBS-3002.

Table 21: CMH Analysis of Composite Responders by Interval (Daily Response Criteria; ITT Analysis Set)

	IBS-3001[a]			IBS-3002[b]		
Interval Treatment	Responder (%)	Non-Responder (%)	*P* value	Responder (%)	Non-Responder (%)	*P* value
Weeks 1 - 4						
Eluxadoline 75 mg BID	20.6	79.4	0.003	25.2	74.8	< 0.001
Eluxadoline 100 mg BID	22.5	77.5	< 0.001	26.7	73.3	< 0.001
Placebo BID	12.9	87.1	---	12.0	88.0	---
Weeks 5 - 8						
Eluxadoline 75 mg BID	26.5	73.5	0.023	31.5	68.5	< 0.001
Eluxadoline 100 mg BID	28.9	71.1	0.002	33.5	66.5	< 0.001
Placebo BID	19.9	80.1	---	19.9	80.1	---
Weeks 9 - 12						
Eluxadoline 75 mg BID	23.7	76.3	0.514	32.3	67.7	0.001
Eluxadoline 100 mg BID	30.3	69.7	0.005	31.9	68.1	0.002
Placebo BID	21.8	78.2	---	22.0	79.1	---
Weeks 13 - 16						
Eluxadoline 75 mg BID	22.7	77.3	0.563	30.7	69.3	0.002
Eluxadoline 100 mg BID	29.1	70.9	0.007	33.8	66.2	< 0.001
Placebo BID	21.1	78.9	---	20.9	79.1	---
Weeks 17 - 20						
Eluxadoline 75 mg BID	27.6	72.4	0.047	31.2	68.8	0.007
Eluxadoline 100 mg BID	28.9	71.1	0.017	31.2	68.8	0.007
Placebo BID	21.8	78.2	---	22.5	77.5	---
Weeks 21 - 24						
Eluxadoline 75 mg BID	27.4	72.6	0.016	28.9	71.1	0.004
Eluxadoline 100 mg BID	28.2	71.8	0.008	32.5	67.5	< 0.001
Placebo BID	20.4	79.6	---	19.9	80.1	---

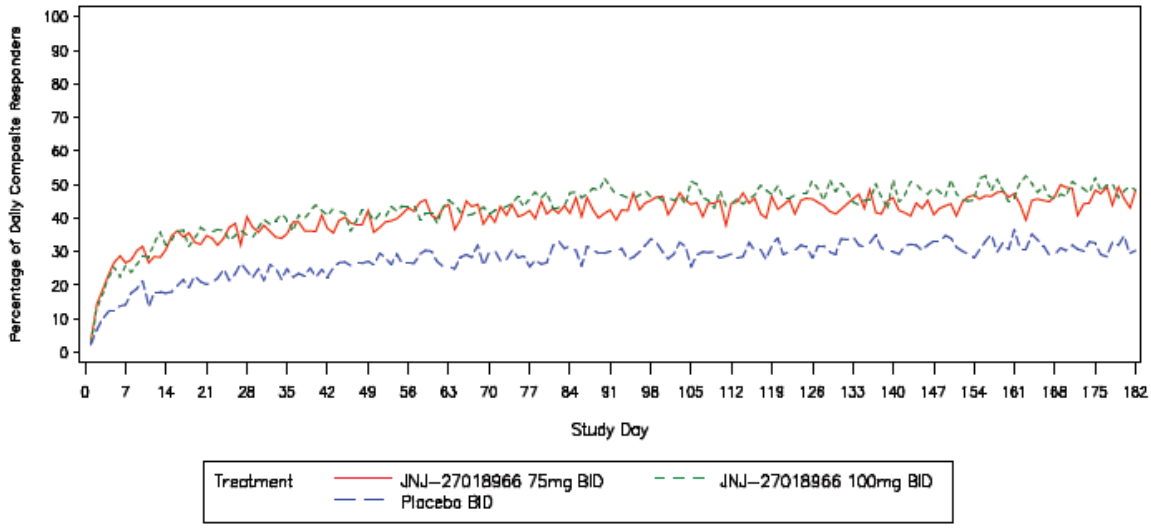
Source: Table 11-7 from Applicant Clinical Study Reports of IBS-3001 and IBS-3002
[a] In Study IBS-3001, eluxadoline 75 mg (N = 427), eluxadoline 100mg (N = 426), placebo (N = 427)
[b] In Study IBS-3002, eluxadoline 75 mg (N = 381), eluxadoline 100mg (N = 382), placebo (N = 382)

Figure 3: Study IBS-3001, Percentage of Daily Composite Responders from Day 1 through Day 182



Source: Copied and electronically reproduced from Applicant's submission, Study IBS-3001 Clinical Study Report, Figure 14.2.1.

Figure 4: Study IBS-3002, Percentage of Daily Composite Responders from Day 1 through Day 182



Source: Copied and electronically reproduced from Applicant's submission, Study IBS-3002 Clinical Study Report, Figure 14.2.1

Reviewer Comments: Both the analysis of composite responders by time interval and the line plots of percentage of daily composite responders show consistently higher composite response rates for the eluxadoline groups compared to placebo, over the entire course of treatment. These differences were statistically significant in both treatment groups in both studies, with the exception of Weeks 9 – 12 and 13 – 16 in

Study IBS-3001, where the 75mg treatment group had a higher proportion of composite responders, but it did not reach statistical significance. These analyses suggest that the effect of eluxadoline is generally durable over 26 weeks of treatment.

Sensitivity Analyses:

The primary endpoint allowed patients who completed 70% of diary entries (60 days) over the 12-week period to be considered for responder analysis, with a patient defined as a composite responder if he or she met the daily response criteria for 50% of those days. A worst-case scenario sensitivity analysis was conducted in both studies to determine if the allowance of missing data based on patient's non-compliance with daily diary entry had an impact on the analysis. These results are shown in **Table 22** below. This analysis required 42 of 84 days to be positive response days for the assessment over Weeks 1 – 12, irrespective of diary compliance. In both **Studies IBS-3001 and IBS-3002**, the proportion of composite responders for both the 75 and 100mg treatment groups was statistically superior to placebo over Weeks 1 – 12 using this worst-case scenario sensitivity analysis approach.

Table 22: Composite Responders, worst case[a]

Treatment	Number (%)		P value[b]
	Responder	Non-responder	
Study IBS-3001			
Weeks 1 – 12			
Eluxadoline 75 mg BID (N = 427)	100 (23.4)	327 (76.6)	0.013
Eluxadoline 100 mg BID (426)	103 (24.2)	323 (75.8)	0.006
Placebo BID (N = 427)	71 (16.6)	356 (83.4)	---
Study IBS-3002			
Weeks 1 – 12			
Eluxadoline 75 mg BID (N = 381)	108 (28.3)	273 (71.7)	< 0.001
Eluxadoline 100 mg BID (N = 382)	108 (28.3)	274 (71.7)	< 0.001
Placebo BID (N = 382)	53 (13.9)	329 (86.1)	---

Source: Tables 14.2.2.3.9 and 14.2.2.3.11 from Complete Study Reports for IBS-3001 and IBS-3002

[a] Composite responder (worst case) is defined a patient who met the daily pain response and the daily stool consistency response criteria for a minimum of 42 days during the 12-week interval

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

In addition, a sensitivity analysis was performed, removing patients who had dose interruptions due to possible or confirmed constipation. This was intended to assess the impact of patients who experienced significant constipation on the overall composite responder endpoint. Only 5 patients from IBS-3001/4 patients from IBS-3002 experienced dose interruptions due to diary-confirmed constipation. These results are shown in **Table 23** below.

Table 23: Composite Responders, Sensitivity Analysis Accounting for Dose Interruptions Due to Constipation[a]

Treatment	Number (%)		P value
	Responder	Non-responder	
Study IBS-3001			
Weeks 1 – 12			
Eluxadoline 75 mg BID (N = 426)	101 (23.7)	325 (76.3)	0.017
Eluxadoline 100 mg BID (423)	107 (25.3)	316 (74.7)	0.004
Placebo BID (N = 426)	73 (17.1)	353 (82.9)	---
Study IBS-3002			
Weeks 1 – 12			
Eluxadoline 75 mg BID (N = 380)	110 (28.9)	270 (71.1)	< 0.001
Eluxadoline 100 mg BID (N = 379)	112 (29.6)	267 (70.4)	< 0.001
Placebo BID (N = 382)	62 (16.2)	320 (83.8)	---

Source: Table 14.2.2.3.7 for CSR IBS-3001 and CSR IBS-3002.
[a] The sensitivity analysis accounting for dose interruptions due to constipation excludes all patients who IVRS have prompted the investigator to call due to no reported bowel movements for 4 consecutive days, this excluded 5 patients from IBS-3001 and 4 patients from IBS-3002.

Sensitivity analyses were also performed to assess the impact of the use of loperamide rescue medication on the composite responder endpoint. In Study IBS-3001, approximately 26% of patients used loperamide rescue medication, and this use was highest in the placebo group (26.9% 75mg, 22.2% 100mg, 28.3% placebo). Similarly, in Study IBS-3002, 30% of overall patients used loperamide, and the use was highest in the placebo group (26.5% 75mg, 29.3% 100mg, 34.6% placebo). **Table 24** below shows the use of loperamide rescue medication in both studies. The Applicant looked at both the subset of patients who did not use loperamide rescue medication during the first 12 weeks of treatment as well as imputing non-response for each day a patient took a dose of loperamide.

Table 24: Loperamide Rescue Medication Use

Treatment	Number (%)	
	Loperamide Use	No Loperamide Use
Study IBS-3001		
Weeks 1 – 12		
Eluxadoline 75 mg BID (N = 427)	115 (26.9)	312 (73.1)
Eluxadoline 100 mg BID (424)	94 (22.2)	330 (77.8)
Placebo BID (N = 427)	121 (28.3)	306 (71.7)
Study IBS-3002		
Weeks 1 – 12		
Eluxadoline 75 mg BID (N = 381)	101 (26.5)	280 (73.5)
Eluxadoline 100 mg BID (N = 382)	112 (29.3)	270 (70.7)
Placebo BID (N = 382)	132 (34.6)	250 (65.4)

Source: created by reviewer from concomitant medications dataset for IBS-3001 and IBS-3002

Table 25: Sensitivity Analyses for Use of Loperamide Rescue Medication

	Study IBS-3001			Study IBS-3002		
Treatment	**N**	**Responder (%)**	**P value[a]**	**N**	**Responder (%)**	**P value[a]**
Weeks 1 - 12						
Patients Not Using Rescue Med						
Eluxadoline 75 mg BID	312	70 (22.4)	0.007	280	86 (30.7)	< 0.001
Eluxadoline 100 mg BID	330	77 (23.3)	0.003	270	77 (28.5)	0.001
Placebo BID	306	43 (14.1)	---	250	42 (16.8)	---
Imputed Non-Response When Rescue Med Used						
Eluxadoline 75 mg BID	427	100 (23.4)	0.013	381	107 (28.1)	< 0.001
Eluxadoline 100 mg BID[b]	424	104 (24.5)	0.004	382	113 (29.6)	< 0.001
Placebo BID	427	71 (16.6)	---	382	62 (16.2)	---

Source: Applicant Integrated Summary of Efficacy, Table 7 - 17

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

[b] Data for patients randomized more than once in an individual study or who were randomized in both Phase 3 studies were only counted once (first randomization). Duplicate data were excluded from the ITT Analysis Set.

Reviewer comments: Results from the worst case scenario sensitivity analyses indicate that that data handling conventions for missing data did not impact results for IBS-3001 or IBS-3002. Similarly, the results of this analysis accounting for dose interruptions due to constipation were consistent with the primary analysis and confirmed that patients experiencing significant constipation did not impact the primary analysis. As previously stated, only 9 patients total (IBS-3001 and -3002) experienced dose interruptions due to constipation. This small number would be unlikely to impact efficacy analyses. The sensitivity analysis imputing non-response for each day a patient took a dose of

loperamide takes into consideration patients who may have used loperamide on a more frequent basis. This reviewer believes that the consistency of these results support the strength of the overall results.

6.1.5 Analysis of Secondary Endpoints(s)

Pain responder:
Pain responders were defined as patients who met the daily pain response criterion for at least 50% of the days and had a minimum of 60 days diary entry for Weeks 1 – 12 and 110 days diary entry for Weeks 1 - 26.

- Daily pain response: worst abdominal pain scores in the past 24 hours improved by ≥ 30% compared to baseline, where baseline was the average of daily worst abdominal pain score the week prior to randomization

The proportion of pain responders (individual pain component of the daily composite responder definition) for the 75mg and 100 mg treatment groups was higher than placebo over the interval from Weeks 1 – 12, as well as over the interval from Weeks 1 – 26 in **both studies IBS-3001 and IBS-3002**, however, the differences did not reach statistical significance. No adjustment for multiple comparisons was made for secondary analyses.

Table 26: Analysis of Pain Responders (ITT Analysis set)

Treatment	Number (%)		P value[a]
	Responder	Non-responder	
Study IBS-3001			
Weeks 1 – 12			
Eluxadoline 75 mg BID (N = 427)	181 (42.4)	246 (57.6)	0.404
Eluxadoline 100 mg BID (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 (426)	198 (46.5)	228 (53.5)	0.284
Placebo BID (N = 427)	185 (43.3)	242 (56.7)	---
Study IBS-3002			
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)	---

Source: Tables 14.2.2.4.7 and 14.2.2.2.1 from CSRs of Study IBS-3001 and Study IBS-3002
[a]P value is based on Chi-square test statistic

Stool consistency responder:
Similarly, stool consistency responders were defined as patients who met the daily stool consistency response criterion for at least 50% of the days and had a minimum of 60 days diary entry for Weeks 1 – 12 and 110 days diary entry for Weeks 1 - 26.

- Daily stool consistency response: BSS score < 5 or the absence of a bowel movement if accompanied by ≥ 30% improvement in worst abdominal pain compared to baseline pain.

In **IBS-3001**, the proportion of stool consistency responders for the 75mg and 100 mg treatment groups was significantly higher than placebo over the interval from Weeks 1 – 12 for both treatment groups, as well as over the interval from Weeks 1 – 26 for the 100mg treatment group. The proportion of stool consistency responders for the 75mg group over the interval from Weeks 1 – 26 was higher than placebo, however, the differences did not reach statistical significance. In **IBS-3002**, the proportion of stool consistency responders for the 75mg and 100mg treatment groups was significantly higher than placebo over both treatment intervals. No adjustment for multiple comparisons was made for secondary analyses.

Table 27: Analysis of Stool Consistency Responders (ITT analysis set)

Treatment	Number (%)		P value[a]
	Responder	Non-responder	
IBS-3001			
Weeks 1 – 12			
Eluxadoline 75 mg BID (N = 427)	128 (30.0)	299 (70.0)	0.008
Eluxadoline 100 mg BID (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 (426)	145 (34.0)	281 (66.0)	0.001
Placebo BID (N = 427)	103 (24.1)	324 (75.9)	---
Study IBS-3002			
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)	---

Source: Applicant CSR IBS-3001 and IBS-3002, Tables 14.2.2.5.6 and 14.2.2.5.8b
[a]P value is based on Chi-square test statistic

IBS-d global symptom responder:
At baseline the average IBS-d global symptom scores **from studies IBS-3001 and IBS-3002** combined were 2.78 (75mg), 2.83 (100mg), and 2.85 (placebo), rated on a scale from 0 to 4, where 0 indicates no symptoms and 4 indicates very severe symptoms. An IBS-d global symptom responder was defined as a patient who met the daily IBS-d global symptom response criterion for at least 50% of days with diary entries during the interval (e.g., Weeks 1 – 12). A daily IBS-d global symptom responder was defined as a patient with a symptom score of 0 (none) or 1 (mild); or a daily IBD-d global symptom score improved by ≥2.0 compared to the Baseline average.

In **Study IBS-3001**, the proportion of IBS-d global symptom responders was higher for the 75mg and 100mg treatment groups compared to placebo over Weeks 1 – 12 and Weeks 1 – 26, however, the only statistically significant difference was over the initial 12 week interval for the 75mg group (P = 0.048). In **Study IBS-3002**, the proportion of IBS-d global symptom responders was statistically higher in both treatment groups over both treatment intervals.

Table 28: IBS-d Global Symptom Responders

Treatment	Number (%)		P value[a]
	Responder	Non-responder	
IBS-3001			
Weeks 1 – 12			
Eluxadoline 75 mg BID (N = 427)	150 (35.1)	277 (64.9)	0.048
Eluxadoline 100 mg BID (426)	148 (34.7)	278 (65.3)	0.063
Placebo BID (N = 427)	123 (28.8)	304 (71.2)	---
Weeks 1 – 26			
Eluxadoline 75 mg BID (N = 427)	155 (363)	272 (63.7)	0.221
Eluxadoline 100 mg BID (426)	158 (37.1)	268 (62.9)	0.144
Placebo BID (N = 427)	138 (32.3)	289 (67.7)	---
Study IBS-3002			
Weeks 1 – 12			
Eluxadoline 75 mg BID (N = 381)	166 (43.6)	215 (56.4)	< 0.001
Eluxadoline 100 mg BID (N = 382)	162 (42.4)	220 (57.6)	< 0.001
Placebo BID (N = 382)	113 (29.6)	269 (70.4)	---
Weeks 1 – 26			
Eluxadoline 75 mg BID (N = 381)	172 (45.1)	209 (54.9)	0.002
Eluxadoline 100 mg BID (N = 382)	165 (43.2)	217 (56.8)	0.012
Placebo BID (N = 382)	131 (34.3)	251 (65.7)	---

Source: Applicant CSR IBS-3001 and IBS-3002, Tables 14.2.2.2.9a and 14.2.2.23
[a] P value is based on chi-square test
CMH analysis using daily response criterion in the ITT analysis set

IBS-AR responders:

Adequate relief (AR) of IBS symptoms was assessed once weekly in the electronic diary by simply responded "yes" or "no" for a given week. A patient was classified as an IBS-AR responder if his or her weekly response was "yes" for 50% or more of the total weeks. **Table 29** below shows the proportion of IBS-AR responders from Study IBS-3001 and IBS-3002.

Table 29: IBS-AR Responders

Treatment	Number (%)		P value[a]
	Responder	Non-responder	
IBS-3001			
Weeks 1 – 12			
Eluxadoline 75 mg BID (N = 427)	226 (52.9)	201 (47.1)	0.008
Eluxadoline 100 mg BID (426)	231 (54.2)	195 (45.8)	0.002
Placebo BID (N = 427)	187 (43.8)	240 (56.2)	---
Weeks 1 – 26			
Eluxadoline 75 mg BID (N = 427)	195 (45.7)	232 (54.3)	0.097
Eluxadoline 100 mg BID (426)	211 (49.5)	215 (50.5)	0.005
Placebo BID (N = 427)	171 (40.0)	256 (60.0)	---
Study IBS-3002			
Weeks 1 – 12			
Eluxadoline 75 mg BID (N = 381)	229 (60.1)	152 (39.9)	0.003
Eluxadoline 100 mg BID (N = 382)	223 (58.4)	159 (41.6)	0.011
Placebo BID (N = 382)	188 (49.2)	194 (50.8)	---
Weeks 1 – 26			
Eluxadoline 75 mg BID (N = 381)	201 (52.8)	180 (47.2)	0.013
Eluxadoline 100 mg BID (N = 382)	205 (53.7)	177 (46.3)	0.006
Placebo BID (N = 382)	167 (43.7)	215 (56.3)	---

Source: Applicant CSR IBS-3001 and IBS-3002, Tables 14.2.3.2.1 and 14.2.3.2.3
[a] P value is based on chi-square test
CMH analysis using in the ITT analysis set

IBS-QoL responders
An IBS-QoL instrument was at each visit, and individual responses to answered items were summed and standardized to a 0 to 100-point scale. A patient was considered an IBS-QoL responder if he or she achieved at least a 14-point improvement in IBS-QoL total score from baseline to the applicable visit.

In **IBS-3001** and **IBS-3002**, for both the 75-mg and the 100-mg treatment groups, the proportion of IBS-QoL total score responders was higher than placebo at each week evaluated through Week 26. In Study **IBS-3001**, this difference was statistically significant for the 100-mg group at Week 4 and 8 only and none of the differences were statistically significant for the 75-mg group. In **IBS-3002**, none of differences were statistically significant.

Other Abdominal Symptoms
Other abdominal symptoms were evaluated during this study, including abdominal bloating and discomfort, and other bowel symptoms were evaluated, including frequency of bowel movements, daily urgency episodes, daily bowel incontinence episodes, and daily incontinence-free days. These results favored eluxadoline in both IBS-3001 and IBS-3002.

Reviewer Comments: Eluxadoline's impact on stool consistency appears to have a greater impact than its impact on abdominal pain, and this is not unexpected, based on the MOA of the product (mixed mu opioid receptor agonist/ delta opioid receptor antagonist). Given the trending towards improvement in the pain response, this reviewer believes the Applicant has demonstrated clinically meaningful change. It does not appear that the Applicant prespecified a hierarchy for evaluation of the secondary efficacy endpoints and did not adjust for multiplicity for secondary endpoints. Results appear to favor eluxadoline for the majority of secondary endpoints, however, statistical significance should not be claimed, given these limitations. Furthermore, the PRO endpoints listed as secondary endpoints (IBS-QoL, IBS-AR, and IBS-d global symptom responder) are exploratory in nature (b) (4)

6.1.5 Other Endpoints

There is no other relevant endpoint information, except as discussed in previous sections of this review.

6.1.7 Subpopulations

The primary endpoint, composite responder, as well as abdominal pain and stool consistency responders were analyzed for each of the subgroups listed below.

- gender
- age (18 to 40, 41 to 64, or ≥ 65)
- geography (US and non-US)
- ethnicity
- race
- BMI
- symptom history (was/wane or persistent)
- h/o GERD
- h/o depression
- refractory to loperamide
- prior cholecystectomy

Gender

The Applicant analyzed the primary endpoint, composite responder, by gender in both studies. In **IBS-3001,** there were 836 female patients and 444 male patients included in the ITT analysis set. Among female patients, the proportion of composite responders from Weeks 1- 12 was higher than placebo for both the 100-mg group and 75-mg groups. This difference was statistically significant only in the 100-mg group. Among

male patients, the proportion of composite responders from Weeks 1- 12 was also higher than placebo for both the 100-mg group and 75-mg groups. However, in the male subgroup this difference was statistically significant only in the 75-mg group. In **IBS-3002**, there were 767 female patients and 378 male patients. The proportion of composite responders from Weeks 1-12 was statistically significantly higher than placebo for both female and male subgroups in both eluxadoline dose groups. The results of the Applicant's subgroup analyses by gender are shown in **Table 30** below.

Table 30: CMH Analysis of Composite Responders[a] by Gender for Weeks 1 – 12

Treatment	Number (%)		P value[b]
	Responder	Non-responder	
IBS-3001			
Male (N = 444)			
Eluxadoline 75 mg BID (N = 151)	39 (25.8)	112 (74.2)	0.006
Eluxadoline 100 mg BID (143)	31 (21.7)	112 (78.3)	0.060
Placebo BID (N = 150)	20 (13.3)	130 (86.7)	--
Female (N = 836)			
Eluxadoline 75 mg BID (N = 276)	63 (22.8)	213 (77.2)	0.287
Eluxadoline 100 mg BID (N = 283)	76 (26.9)	207(73.1)	0.030
Placebo BID (N = 277)	53 (19.1)	224 (80.9)	---
IBS-3002			
Male (N = 378)			
Eluxadoline 75 mg BID (N = 120)	35 (29.2)	85 (70.8)	0.027
Eluxadoline 100 mg BID (N = 126)	40 (31.7)	86 (68.3)	0.008
Placebo BID (N = 132)	23 (17.4)	109 (82.6)	---
Female (N = 767)			
Eluxadoline 75 mg BID (N = 261)	75 (28.7)	186 (71.3)	< 0.001
Eluxadoline 100 mg BID (N = 256)	73 (28.5)	183 (71.5)	< 0.001
Placebo BID (N = 250)	39 (15.6)	211 (84.4)	---

Source: Applicant's Complete Study Reports for IBS-3001 and IBS-3002, Table 14.2.2.3.13
[a] Composite responder = patient who met the daily pain response AND the daily stool consistency response criteria on at least 50% of days during the interval and had for the 12-Week interval a minimum of 60 days of diary data from Weeks 1 – 12.
[b] P value is based on Chi-square test statistic

Reviewer Comments: The subgroup analysis by gender is of particular interest, as the only approved therapy for IBS-D, alosetron, is approved only in women with severe symptoms refractory to other therapies. The subgroup analyses from Studies IBS-3001 and IBS-3002 indicate that eluxadoline is effective in women and men with IBS-D.

Age:
Most patients in Studies IBS-3001 and IBS-3002 (~90%) were less than 65 years of age. **Table 31** below shows the proportion of composite responders in Studies IBS-3001 and IBS-3002 by age.

Table 31: CMH Analysis of Composite Responders by Age for Week 1 - 12

Treatment	Number (%)		P value[b]
	Responder	Non-responder	
IBS-3001			
<65 years			
Eluxadoline 75 mg BID (N = 398)	88 (22.1)	310 (77.9)	0.113
Eluxadoline 100 mg BID (N = 391)	95 (24.3)	296 (75.7)	0.022
Placebo BID (N = 376)	66 (17.6)	310 (82.4)	---
≥ 65 years			
Eluxadoline 75 mg BID (N = 29)	14 (48.3)	15 (51.7)	< 0.001
Eluxadoline 100 mg BID (N = 35)	12 (34.3)	23 (65.7)	0.025
Placebo BID (N = 51)	7 (13.7)	44 (86.3)	---
IBS-3002			
<65 years			
Eluxadoline 75 mg BID (N = 345)	94 (27.3)	251 (72.8)	0.002
Eluxadoline 100 mg BID (N = 343)	99 (28.9)	244 (71.1)	<0.001
Placebo BID (N = 331)	57 (17.2)	274 (82.8)	---
≥65 years			
Eluxadoline 75 mg BID (N = 36)	16 (44.4)	20 (55.6)	<0.001
Eluxadoline 100 mg BID (N = 39)	14 (35.9)	25 (64.1)	0.003
Placebo BID (N = 51)	5 (9.8)	46 (90.2)	---

Source: Applicant Response to Information Request, 25February2015

The Applicant also analyzed efficacy by age further subdividing patients less than 65 into those between 41 and 64 and those less than 18 to 40. Most patients in Studies **IBS-3001** and **IBS-3002** were between 41 and 64 years of age (N = 668 and N = 601 in IBS-3001 and -3002, respectively), followed by 18 to 40 (N = 497 and N = 418) and then ≥ 65 (N = 115 and N = 126). The results in the middle age category were comparable to the overall rates for the study, while the response rates in the younger age group were generally lower and for the older age group were generally higher, when compared to overall rates for the studies. These results are shown in **Table 32** below. In addition, the Applicant pooled the Phase 3 study data and analyzed the proportion of composite responders by age category (<65 and ≥65). In this analysis, the proportions of composite responders were significantly higher than placebo for both eluxadoline doses in both age categories.

Table 32: CMH Composite Responder[a] Proportions by Age Subgroup Week 1 - 12

Treatment	Number (%)		P value[b]
	Responder	Non-responder	
IBS-3001			
Age 18 - 40 (N = 497)			
Eluxadoline 75 mg BID (N = 172)	27 (15.7%)	145 (84.3%)	0.753
Eluxadoline 100 mg BID (N = 166)	34 (20.5%)	132 (79.5%)	0.420
Placebo BID (N = 159)	27 (17%)	132 (83.0%)	---
Age 41 - 64 (N = 668)			
Eluxadoline 75 mg BID (N = 226)	61 (27.0%)	165 (73.0%)	0.023
Eluxadoline 100 mg BID (N = 225)	61 (27.1%)	164 (72.9%)	0.022
Placebo BID (N = 217)	39 (18.0%)	178 (82.0%)	---
Age ≥ 65 (N = 115)			
Eluxadoline 75 mg BID (N = 226)	14 (48.3%)	15 (51.7%)	<0.001
Eluxadoline 100 mg BID (N = 225)	12 (34.3%)	23 (65.7%)	0.025
Placebo BID (N = 217)	7 (13.7%)	44 (86.3%)	---
IBS-3002			
Age 18 - 40 (N = 418)			
Eluxadoline 75 mg BID (N = 139)	28 (20.1%)	111 (79.9%)	0.147
Eluxadoline 100 mg BID (N = 146)	34 (23.3%)	112 (76.7%)	0.037
Placebo BID (N = 133)	18 (13.5%)	115 (86.5%)	---
Age 41 - 64 (N = 601)			
Eluxadoline 75 mg BID (N = 206)	66 (32.0%)	140 (68.0%)	0.005
Eluxadoline 100 mg BID (N = 197)	65 (33.0%)	132 (67.0%)	0.003
Placebo BID (N = 198)	39 (19.7%)	159 (80.3%)	---
Age ≥ 65 (N = 126)			
Eluxadoline 75 mg BID (N = 36)	16 (44.4%)	20 (55.6%)	<0.001
Eluxadoline 100 mg BID (N = 39)	14 (35.9%)	25 (64.1%)	0.003
Placebo BID (N = 51)	5 (9.8%)	46 (90.2%)	---

Source: Applicant's Complete Study Reports for IBS-3001 and IBS-3002, Table 14.2.2.3.13

[a] Composite responder = patient who met the daily pain response AND the daily stool consistency response criteria on at least 50% of days during the interval and had for the 12-Week interval a minimum of 60 days of diary data from Weeks 1 – 12.

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

Reviewer Comments: The results were generally consistent when analyzed by age less than and ≥ 65 years. A higher proportion of patients in both age groups receiving eluxadoline were composite responders compared to placebo. Only the 75 mg treatment arm in patients less than 65 years in Study IBS-3001 failed to reach statistical significance. When further subdividing patients less than 65 into 18 – 40 and 41 – 64, the response rates in the middle age group were comparable to the overall population, and the response rates in the youngest age group were lower than the overall population, particularly in Study IBS-3001. The sponsor provided baseline disease characteristics, presented separately by age category, and no significant differences were noted between groups. This reviewer believes the small sample sizes in these age groups (when further subdividing) make inferences challenging, and given that

these were post-hoc analyses and not controlled for multiplicity, this reviewer believes the data support that eluxadoline is effective across age groups.

Region:
Most patients in the ITT Analysis set were enrolled at sites in the US (N = 1212 in IBS-3001 and N = 1097 in IBS-3002), compared to sites outside the US (N = 68 in IBS-3001 and N = 48 in IBS-3002). The results in the US thus, mirror the overall results, and little can be said about the specific results outside the US, given the small number of patients.

Ethnicity:
The Applicant performed a CMH analysis of composite responders by ethnicity for the pooled Phase 3 studies. In the pooled ITT Analysis Set, 659 patients self-identified as Hispanic or Latino, and 1764 patients did not. In this analysis, the proportions of composite responders were significantly higher than placebo for both eluxadoline doses in both ethnicity categories over Weeks 1 – 12.

Race:
In the pooled ITT Analysis set, 2084 patients self-identified as white, 277 patients were black, and 62 patients were another race. The proportion of composite responders was higher than placebo for both eluxadoline doses among patients who were white and black. These differences were not statistically significant among patients who were black; however, the sample size for this group was small, so it is difficult to interpret the results.

BMI:
The Applicant performed a CMH analysis of composite responders by BMI category (<30 and ≥30 kg/m^2) for the pooled Phase 3 studies. In the pooled ITT Analysis Set, 1276 patients had a BMI < 30 kg/m^2 and 1142 patients had a BMI ≥30 kg/m^2. In this analysis, the proportions of composite responders were significantly higher than placebo for both eluxadoline doses in both BMI categories over Weeks 1 – 12.

Baseline Characteristics and Other Medical History:
The pooled Phase 3 study results were consistent and favored eluxadoline when analyzing the proportion of composite responders by baseline disease characteristics. Similarly, the Applicant performed subgroup analyses on patients who were refractory to loperamide, as well as patients with a history of GERD, history of depression, and prior cholecystectomy. The proportion of composite responders was consistently higher in the eluxadoline dose groups than placebo over Weeks 1 – 12, though this did not always reach statistical significance.

Reviewer Comments: While the sample sizes were small for many of the subgroups analyzed, this reviewer believes the results of the subgroup analyses were consistent across a variety of subpopulations and indicate that eluxadoline is effective across a

variety of subgroups.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Study IBS-2001 was a 12-week, double-blind, placebo-controlled, parallel-group, dose-ranging, Phase 2 study of eluxadoline in 807 patients meeting the Rome III diagnostic criteria for IBS-d. IBS-2001 was designed to evaluate the clinical response relative to placebo of 4 different doses of eluxadoline: 5mg BID, 25mg BID, 100mg BID, and 200mg BID.

As shown in **Table 33** below, **Study IBS-2001** demonstrated that patients treated with eluxadoline 100 mg BID and 200 mg BID were twice as likely as placebo patients to achieve study response based on a *post hoc* analysis using the response definitions used in phase 3 studies. (The prespecified primary endpoint of clinical response was defined as meeting BOTH IBS-d improvement-from-baseline criteria: average daily pain score over the past week improved by ≥ 30% and at least 2 points and BSS consistency score of 3 or 4 on > 66% of reported days in past week and did not that evaluate efficacy data over the entire12 weeks.)

Table 33: Study Response Rates Based on *Post Hoc* Daily Responder Definition: IBS-2001

	Eluxadoline 5 mg BID N = 105	Eluxadoline 25 mg BID N = 167	Eluxadoline 100 mg BID N = 163	Eluxadoline 200 mg BID N = 160	Placebo N = 159
Weeks 1 – 12					
Overall response rate	13.3%	16.9%	28.0%	28.5%	13.8%
Odds ratio	0.96	1.28	2.43	2.50	---
(95% CI)	(0.47, 1.95)	(0.70, 2.32)	(1.38, 4.28)	(1.42, 4.40)	---
P value	0.911	0.426	0.002	0.002	---

Source: Applicant Clinical Study Report IBS-2001, Table 11-7
Note: The ITT Analysis Set for this study excluded patients from Site 191 that were terminated by Furiex and reported to the FDA for potential scientific misconduct. Response rates and odds ratios are based on model estimates from the logistic regression. Patients were included in the interval of Weeks 1-4, Weeks 5-8, or Weeks 9-12 if they received at least 1 dose of study medication within that interval.

The 100mg BID dose was selected for Phase 3 studies, as the 200mg BID dose did not appear to improve post hoc response rates over the 100mg BID dose, and there was a slight increase in gastrointestinal AEs at the higher dose. The 75mg BID dose was included in Phase 3 studies based on efficacy trends in Phase 2 studies and a favorable safety profile.

In **Study IBS-3001 and IBS-3002**, both the 75mg BID and the 100mg BID doses were statistically superior to placebo for the primary endpoint of composite response over Weeks 1 – 12. When looking at all intervals of analysis, however, the results for 100mg BID appeared more robust than the 75mg BID dose. See **Table 20** and **Table 21**, above.

Reviewer Comments: This reviewer agrees with the dose selection, based on both phase 2 and phase 3 data suggesting that 100mg BID dose provides additional efficacy when compared to 75mg BID but may have an improved safety profile when compared to 200mg BID.

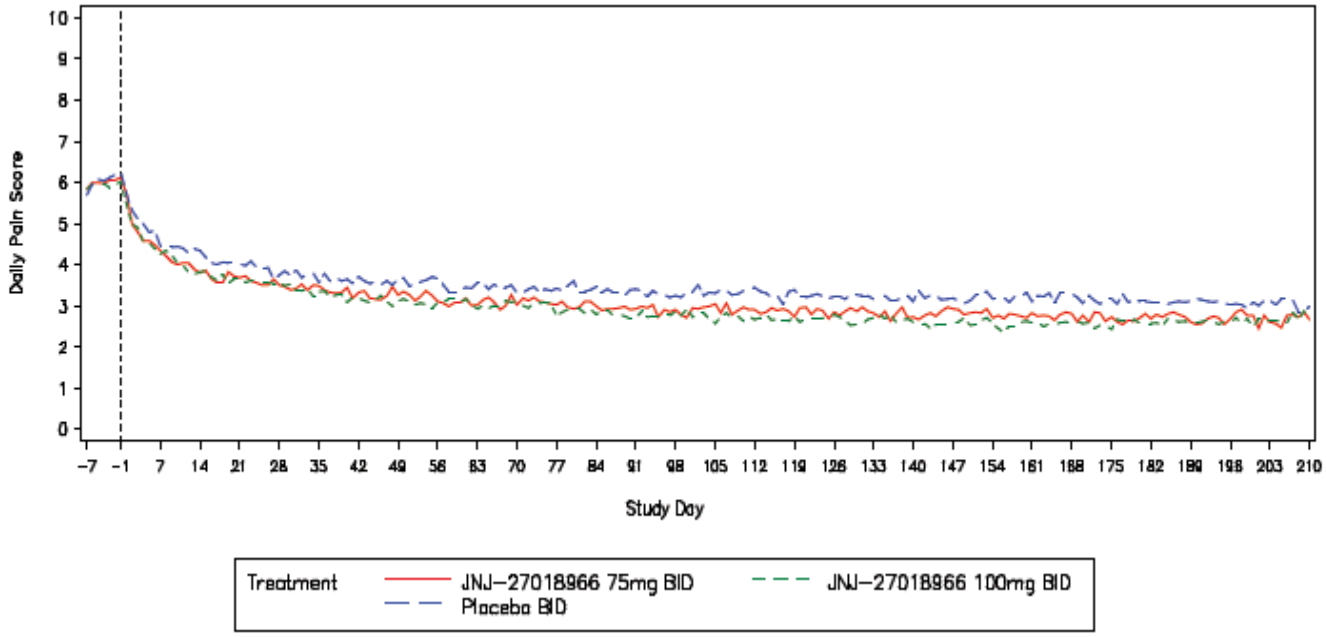
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Please see Section 6.1.4 for a discussion of durability of treatment through 26 Weeks. Efficacy beyond 26 weeks was not assessed in either IBS-3001 or IBS-3002.

6.1.10 Additional Efficacy Issues/Analyses

Study IBS-3002 included a 4-week blinded withdrawal period, to assess for significant worsening or "rebound" of symptoms following cessation of therapy. **Figure 5** below provides a line plot of daily pain scores which indicate that average daily pain scores remained lower for the eluxadoline treatment groups than for placebo during the 4-week blinded withdrawal period.

Figure 5: Line Plot of Daily Pain Scores from IBS-3002, Including Weeks 27 - 30



Source: Copied and electronically reproduced from Applicant's submission, Study IBS-3002 Clinical Study Report, Figure 14.2.4.

The Applicant provided a summary of weekly stool consistency scores and this information is provided below in **Table 34** for weeks 26 through 30.

Table 34: Summary of Weekly Stool Consistency Scores Weeks 26 – 30 for IBS-3002

	Eluxadoline 75 mg BID N = 381	Eluxadoline 100 mg BID N = 382	Placebo BID N = 382
Week 26 (n)	255	267	267
Mean (SD)	4.39 (1.471)	4.26 (1.401)	5.05 (1.237)
Median	4.50	4.30	5.20
Week 27 (n)	253	252	258
Mean (SD)	4.55 (1.441)	4.45 (1.333)	4.90 (1.280)
Median	4.90	4.70	5.00
Week 28	247	249	253
Mean (SD)	4.53 (1.449)	4.48 (1.343)	4.90 (1.314)
Median	4.90	4.70	5.00
Week 29 (n)	242	243	253
Mean (SD)	4.57 (1.468)	4.51 (1.367)	4.88 (1.317)
Median	4.80	4.70	5.00
Week 30 (n)	228	241	241
Mean (SD)	4.57 (1.443)	4.54 (1.352)	4.88 (1.319)
Median	4.80	4.80	5.00

Source: Adapted from Applicant Clinical Study Report IBS-3002, Table 14.2.1.2

Reviewer Comments: There was no prespecified endpoint assessing for rebound symptoms during the 4-week blinded withdrawal. However, it does not appear that there was a rapid and significant worsening of either abdominal pain or diarrheal symptoms during this time period. Stool consistency scores did appear to worsen, as would be expected on cessation of therapy, but this did not appear to occur abruptly. This reviewer does not believe any language related to rebound is needed in the labeling, based on the data provided.

7 Review of Safety

Safety Summary

Based on the safety data reviewed from the eluxadoline clinical development program, this medical reviewer finds that the eluxadoline represents an acceptable risk for the treatment of adults with IBS-D, and that no formal postmarketing Risk Evaluation and Mitigation Strategy (REMS) is required for eluxadoline.

A total of 2562 subjects have been exposed to eluxadoline during the clinical development program, including 520 and 541 patients exposed to 6 months of 75mg and 100mg BID treatment, respectively. In addition, over 340 patients were exposed to 12 months of treatment with eluxadoline75mg or 100mg BID. Eluxadoline was generally well tolerated, and the overall incidence rates for AEs were comparable across treatment groups. There was an increased risk of adverse events associated with Sphincter of Oddi dysfunction with eluxadoline. These events (pancreatitis and hepatobiliary events) completely resolved on discontinuation of therapy. The most common AEs reported were within the GI disorders SOC. Constipation occurred more commonly in eluxadoline treatment arms, and there was a slightly higher incidence of abdominal pain in the eluxadoline treatment arms compared to placebo early in the course of treatment. There appeared to be a slightly higher incidence of abdominal pain in patients receiving 100mg eluxadoline compared with 75mg eluxadoline and placebo, and this was particularly evident in patients with a prior cholecystectomy. Most of these AEs of abdominal pain occurred early in the course of treatment. These AEs appeared to resemble mild AEs associated with sphincter of Oddi spasm, particularly given their association with cholecystectomy status. The Applicant proposes marketing the 75mg dose for patients who have had a prior cholecystectomy or who cannot tolerate the 100mg dose. Given the 75mg was demonstrated to be effective and there is the potential for increased abdominal pain with the 100mg dose, particularly in patients with prior cholecystectomy, this reviewer believes this is an acceptable approach.

There were no deaths, and serious adverse events were uncommon and the proportion of patients with SAEs was similar across treatment arms (4.2% 75mg, 4.0% 100mg, 2.6% placebo). There was no imbalance of AEs suggestive of abuse potential and no indication of symptoms related to withdrawal on discontinuation of eluxadoline.

See also the risk benefit assessment in Section 1.2.

7.1 Methods

The safety analysis set was defined as all patients enrolled who received at least one dose of study drug. Any analysis based on the safety analysis set was based on the treatment actually received. As described in Section 6.1.3, a total of 58 patients randomized to eluxadoline 75mg BID in Study IBS-3001 were impacted by an IVRS treatment misallocation during the study. These patients were incorrectly dispensed 100mg at their Week 18 visit and 53 of these patients took the wrong treatment for 1 to 131 days. For each of these patients, an affected study day window was identified (i.e., when the patient was taking the incorrect medication), and safety data that were recorded during the affected study day window were presented in summary tables according to the treatment being taken at that time. These patients were included in

both treatment arms of the Safety Analysis Set. The impact of these misallocations on the safety analysis sets in Phase 3 studies is shown in **Table 35** below.

Table 35: Randomized and Safety Analysis Set from Phase 3 Studies

Analysis Set	IBS-3001				IBS-3002			
	Eluxadoline 75 mg BID	Eluxadoline 100 mg BID	Placebo BID	Total	Eluxadoline 75 mg BID	Eluxadoline 100 mg BID	Placebo BID	Total
Randomized Set	428	426	427	1281	381	383	382	1146
Safety Analysis Set	428	479[a]	427	1276	379	380	381	1137

Source: Table 11-1 of Clinical Study Report IBS-3001 and Table 11-1 of Clinical Study Report IBS-3002
[a] The safety analysis set in the 100-mg eluxadoline group for IBS-3001 includes 53 patients randomized to the 75mg group who received eluxadoline 100mg in error for 1 to 131 days due to a systemic error in the IVRS system.

The analysis of this safety review is based on the ISS datasets provided by the Applicant and focuses on the 75mg, 100mg, and placebo treatment arms from Studies IBS-2001, IBS-3001, and IBS-3002, as the patient populations for these studies were similar. The Applicant's Safety Analysis Set and MO's Safety Analysis Set, based on the ISS datasets, are provided in **Table 36** below.

Table 36: Applicant and MO ISS Safety Analysis Set from Phase 2 and 3 Studies

Analysis Set	Eluxadoline 75 mg BID	Eluxadoline 100 mg BID	Placebo BID	Total
Applicant's Safety Analysis Set[a]	807	1032	975	2814
MO's Safety Analysis Set	803	976	972	2751

Source: Sponsor ISS and MO analysis using ISS datasets
[a] The Applicant's Safety Analysis Set for the combined Phase 2 and 3 studies includes a limited number of patients in more than one treatment arm due to study drug misallocation.

Reviewer Comment: This reviewer agrees with recording AEs according to the actual treatment taken at the time of the AE. However, the Applicant counted patients twice when determining the denominator for AE incidence rates. This reviewer was unable to duplicate this analysis strategy using the datasets provided. To check the Applicant's presentation of safety findings, separate analyses were run using the ISS dataset and counting patients according to the actual drug taken at the time of the AE, however, the denominator included patients only in 1 treatment arm, according to their planned/randomized treatment. Results were compared with the results from the Applicant, and any discrepancies are noted throughout the review.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were reviewed primarily from double-blind, placebo controlled studies IBS-2001, IBS-3001 and IBS-3002. The focus of the safety review was on the doses

studied in the Phase 3 Studies (75mg BID and 100mg BID), however, for certain AEs of interest (e.g., pancreatitis), all doses were included in the analysis.

Table 37: Description of Phase 2 and 3 Studies Primarily Reviewed in Safety Review

Clinical Trial	Trial Design/No of Centers	Trial Population	Treatment Arms	Number of patients by treatment entered/completed	Gender M/F Median Age (Range)	Primary Efficacy Endpoint
IBS-2001	Randomized, double-blind, parallel-group, placebo control, dose ranging study/ 208 centers in US	Adults (18 – 65) with IBS-d and 1 week prior to randomization: - average daily pain scores ≥3.0 -average BSS ≥5.5 -diary compliance	Eluxadoline: 5 mg PO BID 25 mg PO BID 100 mg PO BID 200 mg PO BID Placebo	111/50 174/131 176/123 174/103 172/118	246/561 46 years (18 – 65)	Study composite response over Weeks 1 – 12 *(post hoc)*
IBS-3001	Randomized, double-blind, placebo control/ 295 centers in US, Canada, and UK	Adults with IBS-d and 1 week prior to randomization: - average daily pain scores ≥3.0 -average BSS ≥5.5 and ≥ 5 days with a BSS score ≥ 5 IBS-d global symptom score ≥ 2 -diary compliance	Eluxadoline: 75 mg BID 100 mg BID Placebo	429/257 426/257 427/269	444/838 45 years (18 – 80)	Proportion of composite responders for Weeks 1 – 12 (FDA) and Weeks 1 – 26 (EMA)
IBS-3002	Randomized, double-blind, placebo control/ 208 centers in US	Adults (18 – 60) with IBS-d and 1 week prior to randomization: - average daily pain scores ≥3.0 -average BSS ≥5.5 and ≥ 5 days with a BSS score ≥ 5 IBS-d global symptom score ≥ 2 -diary compliance	Eluxadoline: 75 mg BID 100 mg BID Placebo	381/250 383/264 382/273	378/768 45.5 years (18 – 77)	Proportion of composite responders for Weeks 1 – 12 (FDA) and Weeks 1 – 26 (EMA)

Source: Applicant's Integrated Summary of Safety, Table 4-1

7.1.2 Categorization of Adverse Events

An adverse event (AE) was defined as any untoward medical occurrence in a study patient administered a pharmaceutical product which does not necessarily have a causal relationship to study medication. Adverse events were classified by the Applicant using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, version 11.0, and classified by MedDRA system organ class (SOC) and preferred term (PT).

All AEs reported or observed from the time a patient receives the first dose of study drug through the follow-up visit were recorded in the AE page of the eCRF. In addition to patient observations, AEs were collected from other sources including laboratory values, physical examination findings, and ECG changes. All AEs are recorded in the eCRF. Patient responses to certain questions from the IBS-QoL instrument were also prospectively considered AEs for the purposes of statistical analyses, though they were not captured on the eCRF.

Investigators assessed the intensity of AEs using the criteria shown in **Table 38**. In addition, investigator assessed the relationship or association of the study medication in causing or contributing to the AE using the following classification: definite, probable, possible, unlikely, or not related.

Table 38: AE Severity Criteria

Severity	Definition
Mild	These events require minimal or no treatment and do not interfere with the patient's daily activities.
Moderate	These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe	These events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Source: Reviewer's Table from Applicant's Clinical Study Reports for Studies IBS-3001 and IBS-3002

The applicant's categorization of adverse events was assessed by comparing the verbatim terms to the preferred terms used by investigators and subjects in both Phase 3 Studies. Some splitting of terms related to AEs of interest occurred as noted here, and these were combined in certain analyses throughout Section 7.

- Combined abdominal pain, abdominal pain lower, and abdominal pain upper to ABDOMINAL PAIN to assess for AEs of abdominal pain
- Combined ALT increased, hepatic enzyme abnormal, AST increased, transaminases increased in analyses of liver injury
- Combined pancreatitis and pancreatitis acute
- Combined melena, hematochezia, rectal hemorrhage to assess for increased risk of ischemic colitis

Reviewer Comment: The Applicant's categorization of adverse events was adequate as assessed by this reviewer's comparison of verbatim terms to dictionary derived terms. Some splitting of symptoms related to abdominal pain as well as hepatic enzymes occurred as shown above, and this is addressed further throughout the safety review. The Applicant incorrectly listed the MedDRA version as 11.1 in the Define.XML file; the correct version is 11.0.

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

Data from the phase 2 dose-ranging study (IBS-2001) and two phase 3 studies (IBS-3001 and IBS-3002) were combined and analyzed for the integrated safety evaluation. The treatment groups presented in summary tables and figures in the ISS included:

Table 39: Treatment Groups from Phase 2 and 3 Studies

Treatment Group	Contributing Studies
Eluxadoline 5 mg	IBS-2001
Eluxadoline 25 mg	IBS-2001
Eluxadoline 200 mg	IBS-2001
Eluxadoline 75 mg	IBS-3001, IBS-3002
Eluxadoline 100 mg	IBS-2001, IBS-3001, IBS-3002
Placebo	IBS-2001, IBS-3001, IBS-3002

Source: Applicant's Integrated Summary of Safety

Discussions of the pooled data in this review focus on the 75 mg BID and 100 mg BID eluxadoline doses from Studies IBS-2001, IBS-3001, and IBS-3002.

Reviewer Comments: The pooling of data as presented in the Applicant's integrated summary of safety is acceptable to this reviewer, as the patients from these studies are believed to be sufficiently similar.

7.2 Adequacy of Safety Assessments

The safety of eluxadoline was assessed throughout the clinical development program through the monitoring of AEs, 12-lead ECGs, physical examination findings, vital signs measurements, clinical laboratory assessments, the Subjective Opiate Withdrawal Scale, concomitant medications, and pregnancy tests for women.

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

A total of 2562 subjects have received at least 1 dose of oral eluxadoline during the clinical development program. This includes 2232 patients with IBS-d in the phase 2 and phase 3 studies and 330 subjects in phase 1 oral administration studies. An additional 33 subjects were exposed to at least 1 dose of intranasal eluxadoline during the intranasal abuse potential study. A total of 1032 patients received at least 1 dose of 100 mg eluxadoline and 803 patients received at least 1 dose of 75 mg eluxadoline, the proposed doses for marketing. **Table 40** shows a summary of duration exposure to eluxadoline for the pooled phase 2 and 3 studies, where exposure was defined as the total days the patient was exposed to study drug, excluding any days where it was recorded that an interruption had occurred.

Table 40: Duration of Exposure (Safety Analysis Set) – Pooled Analysis Phase 2 and Phase 3

	Eluxadoline 75 mg BID N[a] = 807	Eluxadoline 100 mg BID N[a] = 1032	Placebo BID N[a] = 975
N	803	1032	972
Mean (SD)	211.6 (121.80)	186.0 (123.42)	190.9 (121.28)
Median	183.0	183.0	183.0
Min, Max	1, 384	1, 399	1, 390
Duration of exposure by interval, n (%)			
n[b]	803	976	972
≥ 1 day	803 (100%)	976 (100%)	972 (100%)
≥ 1 week	781 (97.3%)	944 (96.7%)	959 (98.7%)
≥ 4 weeks	743 (92.5%)	884 (90.6%)	913 (93.9%)
≥ 12 weeks	662 (82.4%)	763 (78.2%)	777 (79.9%)
≥ 26 weeks	520 (64.8%)	541 (55.4%)	533 (54.8%)
≥ 52 weeks	176 (21.9%)	170 (17.4%)	183 (18.8%)

Source: Table 8 – 2 Applicant Integrated Summary of Safety and Applicant's Response to Information Request dated 02Dec2014

Exposure was defined as the total days the patient was exposed to study drug, excluding any days where it was recorded that an interruption had occurred. If the last dose date was missing or incomplete, the following steps were implemented to impute the exposure duration: (1) If the latest kit dispensed had a complete return date, the return date to calculate exposure was used. (2) If the partial information on the last dose date was UK-MMM-YYYY, the last day of the appropriate month as the end date was assumed. (3) Otherwise, the latest kit dispensed date and the number of tablets was used to impute an end date assuming the patient took the tablets with 100% compliance, i.e., divided the total tablets by 4 to determine the number of days and added this to the dispensed date.

[a] N reflects the safety analysis dataset and includes all patients who received at least 1 dose of study drug (i.e., the number of patients randomized + number of patients who received the treatment due to IVRS/IWRS misallocation or site misallocation)

[b] n used in the determination of duration of exposure by interval does not include patients who received study drug due to IVRS/IWRS misallocation or site misallocation.

Reviewer Comments: The applicant's safety database exceeds the ICH E1A recommendations for drugs that are to be used chronically (reference: ICH E1A Guidance "The Extent of Population Exposure to Assess Clinical Safety: For Drugs

Intended for Long-term Treatment of Non-Life-Threatening Conditions" available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073083.pdf). The overall exposure to eluxadoline and duration of clinical trials during clinical development were acceptable to assess the safety of the product.

7.2.2 Explorations for Dose Response

The Applicant explored 4 eluxadoline doses compared with a placebo arm in a Phase 2 Dose-Ranging Study: 5, 25, 100, or 200 mg BID. The 5mg group was deselected at a planned interim analysis for lack of efficacy, and 3 doses continued through a 12-week double-blind treatment phase and 2-week post-treatment phase. Study IBS-2001 demonstrated that patients treated with eluxadoline 100 mg BID and 200 mg BID were twice as likely as placebo patients to achieve study response based on a post hoc analysis using the response definitions used in phase 3 studies. The 100mg BID dose was selected for Phase 3 studies, as the 200mg BID dose did not appear to improve post hoc response rates over the 100mg BID dose, and there was a slight increase in gastrointestinal AEs at the higher dose, as shown in **Table 41** below. The 75mg BID dose was included in Phase 3 studies based on efficacy trends in Phase 2 studies and a favorable safety profile, thus 75mg and 100mg BID were selected for Phase 3 Studies.

Table 41: TEAEs reported by at least 5% of Patients in 100 or 200mg Treatment Group, IBS-2001

	Eluxadoline 100 mg BID N = 165	Eluxadoline 200 mg BID N = 172	Placebo BID N = 159
Total number of TEAE	167	233	174
Number of patients with at least 1 TEAE	73 (44.2)	90 (52.3)	78 (49.1)
System Organ Class, n (%)			
Gastrointestinal disorders	35 (21.2)	48 (28.0)	25 (15.7)
Infections and infestations	29 (17.6)	24 (14.0)	32 (20.1)
Nervous	13 (7.9)	24 (14.0)	11 (6.9)
Musculoskeletal and connective tissue disorders	14 (8.5)	12 (7.0)	16 (10.1)
General disorders and administration site conditions	4 (2.4)	15 (8.7)	6 (3.8)

Source: Applicant Clinical Study Report, IBS-2001, Table 12-3

The adverse event rates were similar between dosing groups, when looking at the data from pooled Phase 2 and 3 Studies. Specifically, 54.7% of patients in placebo arms from Phase 2 and 3 studies experienced one or more AE, compared to 55.7% in the 100mg BID group and 60.2% in the 75mg BID group. There were more SAEs and AEs leading to discontinuation in the eluxadoline treatment arms, compared with placebo,

though these event rates were similar between the two active treatment arms and no clear safety dose-response relationship was observed. There did appear to be a slight increase in gastrointestinal AEs at the higher dose.

Table 42: Overview of Adverse Events – Pooled Phase 2 and 3 Studies, All Doses

n (%)	Eluxadoline 5 mg BID[a] N = 109	Eluxadoline 25 mg BID N = 173	Eluxadoline 75 mg BID N[b] = 807	Eluxadoline 100 mg BID N[b] = 1032	Eluxadoline 200 mg BID N = 171	Placebo BID N[b] = 975
Adverse events	48 (44.0)	86 (49.7)	486 (60.2)	575 (55.7)	91 (53.2)	533 (54.7)
Serious adverse events	1 (0.9)	3 (1.7)	34 (4.2)	41 (4.0)	3 (1.8)	25 (2.6)
Adverse events leading to discontinuation	2 (1.8)	5 (2.9)	67 (8.3)	80 (7.8)	22 (12.9)	42 (4.3)

Source: Applicant ISS Amendment Tables 2.16 and 2.49

[a] The eluxadoline 5mg BID treatment group was deselected for lack of efficacy at a planned interim analysis in IBS-2001 and patients in that arm were discontinued

[b] Numbers reflect Applicant's safety analysis set; patients who were misallocated treatment are included in the denominator for both treatment arms

Please see section 6.1.8, Analysis of Clinical Information Relevant to Dosing Recommendations, as well as the Clinical Pharmacology and Pharmacometrics reviews for additional details and assessment of the exposure-response relationship.

7.2.3 Special Animal and/or In Vitro Testing

None

7.2.4 Routine Clinical Testing

Individual clinical trial protocols outlined safety monitoring and included assessment of AEs, serious AEs, and deaths, as well as the following specific safety related testing:

- Clinical laboratory testing was conducted as specified in individual study protocols and included
  - Hematology: WBC with differential, hemoglobin, hematocrit, platelet count, red blood cell count, MCV, MCH, MCHC
  - Serum chemistry: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, carbon dioxide, calcium (albumin corrected), chloride, creatinine, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, total protein, and serum lipase.
  - Serum/urine pregnancy in female patients of childbearing potential
- Vital signs were generally collected at each study visit

- Physical examination were conducted at periodic visits beginning at prescreening and through the follow-up visit
- Electrocardiogram was conducted at periodic visits beginning at prescreening and through the follow-up visit
- Subjective opiate withdrawal scale

Reviewer comment: The clinical testing performed as part of routine safety assessments was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Eluxadoline is not metabolized and is cleared primarily via the biliary system, with < 1% excreted by the kidneys. The only minor and inactive metabolite is the acyl glucuronide metabolite (M11) which was detected in the urine, but not in the systemic circulation, following 1000mg oral doses in healthy volunteers.

Eluxadoline did not induce or significantly inhibit CYP enzymes in vitro in primary human hepatocytes and human liver microsomes. In in vitro studies, eluxadoline was transported by OAT3, OATP1B1, and BSEP, however, it did not inhibit any drug transporters with the exception of OATP1B1 (32.6% inhibition) and P-gp (6.3% inhibition). Study CPS-1001 was a clinical drug-drug-interaction study assessing the impact of coadministration of eluxadoline with cyclosporine and probenecid (OATP1B1 inhibitors). Coadministration of eluxadoline with cyclosporine increased eluxadoline exposure by approximately 5-fold in drug-drug interaction studies. This is discussed further in Section 7.5.5 Drug-Drug Interactions. The Applicant also assessed the impact of coadministration of oral-contraceptives with eluxadoline. Study CPS-1007 demonstrated that there is no clinically meaningful drug interaction between eluxadoline and Brevicon.

Please refer to the Clinical Pharmacology Review.

Reviewer comment: The label currently states that the (b) (4) .
This reviewer agrees with the proposed labeling.

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

Adverse events of special interest related to the pharmacologic class of eluxadoline include AEs related to sphincter of Oddi (SO) spasm, including pancreatitis and hepatobiliary events; constipation events, especially severe complications of constipation; events of fall, syncope, and road traffic accidents, and special considerations related to abuse and withdrawal potential.

Sphincter of Oddi Spasm: SO spasm is an established class effect associated with μOR agonists. SO spasm is typically temporary and rapidly reversible, presenting as pancreatitis or abdominal or biliary-type pain with or without abnormal liver enzyme tests. In order to evaluate potential AEs related to the sphincter of Oddi, the Applicant established an external Hepatobiliary and Pancreatitis Adjudication Committee (HPAC) to evaluate all suspected cases of SOD and determine if blinded AEs in IBS-3001 and IBS-3002 met prespecified case definitions for pancreatitis and acute hepatobiliary events, and to determine the potential etiology of SO spasm in these events. Cases were identified first using an expansive prospectively established list of MedDRA terms relating to suspected acute pancreatic or hepatic obstruction. These AEs were further screened by the CRO and those meeting specific clinical criteria (e.g., drug withdrawn) were submitted for adjudication by the committee. The following case definitions were used:

- Acute pancreatitis was defined as having at least 2 of the following 3 features:
  - Abdominal pain suggestive of pancreatitis (epigastric pain often radiating to the back), with the start of such pain considered to be the onset of acute pancreatitis;
  - Serum amylase or lipase levels ≥ 3x ULN
  - Characteristic findings on CT, MRI, or transabdominal US
- Acute hepatobiliary event was defined as consisting of all of the following 3 criteria:
  - Abdominal pain suggestive of biliary origin (epigastric or RUQ pain) with the start of such pain considered to be the onset of the acute hepatobiliary event
  - Serum ALT or AST ≥ 3x ULN, or 2x an elevated baseline value (if that value is > 3x ULN)
  - Event prompts study drug withdrawal
- Sphincter of Oddi spasm was defined as an acute reversible pancreatic or biliary tract obstruction

Constipation Related Adverse Events:
Constipation adverse events were spontaneously recorded during patient visits, along with other adverse events occurring during the course of treatment. Adverse events of constipation were also prospectively defined based on patient's daily IVRS entries related to bowel movements and stool consistency during the time the IVRS system was maintained (i.e., during the first 26 weeks of treatment in studies IBS-3001 and IBS-3002). IVRS-confirmed constipation was defined as:

- Prospectively: The absence of bowel movement on 4 consecutive days as confirmed by non-missing IVRS diary entries
- Retrospectively: An average BSS score < 2 over any study week based on IVRS diary entries.

Abuse Potential:

To assess the relative abuse potential for eluxadoline, the sponsor conducted nonclinical and clinical abuse potential studies. In addition, the sponsor analyzed AEs potentially related to abuse for the pooled Phase 2 and 3 studies and for Phase 1 studies which were not designated to evaluate abuse potential. The Applicant derived a list of PTs possibly related to abuse potential included: dizziness, fatigue anxiety, depression, somnolence, hypoesthesia, paresthesia, asthenia, lethargy, nervousness, sedation, abnormal dreams, euphoric mood, feeling drunk, restlessness, affective disorder, agitation, depressed mood, disturbance in attention, emotional distress, energy increased, memory impairment, mood swings, and nightmare.

Withdrawal Potential:
In addition to routine AE surveillance, the Subjective Opiate Withdrawal Scale (SOWS) was used to screen for any potential withdrawal effects in Study IBS-3002. The SOWS includes 16 withdrawal symptoms, each having a possible score of 0 to 4 with 0 = not at all and 4 = extremely. Patients in Study IBS-3001 were asked to complete the SOWS at Week 52 or at early withdrawal. For Study IBS-3002, the SOWS was only completed for patients who discontinued prior to completion of the double-blind treatment period. Patients who completed the blinded withdrawal period were not asked to complete the SOWS, in order to maintain the blinding for the single-blind placebo washout period.

Reviewer comment: This reviewer believes the Applicant does a thorough job of evaluating potential adverse events related to the pharmacologic class of eluxadoline.

7.3 Major Safety Results

Table 43: Applicant Overview of Adverse Events from Pooled Phase 2 and 3 Studies

	Eluxadoline 75 mg BID N = 807		Eluxadoline 100 mg BID N = 1032		Placebo BID N = 975	
	n (%)	Events	n (%)	Events	n (%)	Events
Adverse events	486 (60.2)	1556	575 (55.7)	1804	533 (54.7)	1573
Serious AEs	34 (4.2)	40	41 (4.0)	65	25 (2.6)	28
Related serious AEs	5 (0.6)	5	5 (0.5)	7	0	0
Deaths[a]	0	0	0	0	0	0
AEs leading to discontinuation	67 (8.3)	68	80 (7.8)	84	42 (4.3)	46

Source: From Applicant ISS Amendment Tables 2.16 and 2.49
[a] one patient death (Patient IBS-3001 138/0001) was reported after the date of the patient's last study visit. This death is not included as a death while participating in a study. This patient narrative is summarized in Section 7.3.1 Deaths.

Reviewer Comments: The Applicant's approach to categorizing patients with IVRS or study site drug misallocations was to include patients in whichever treatment group

(dose) they were on when the adverse event occurred. So patients who were randomized to 75mg but incorrectly received 100mg due to IVRS misallocation would have been counted as their actual treatment received at the time of a TEAE. This is a reasonable approach, however, the Applicant includes these patients twice in the denominator (i.e., includes misallocated patients in both treatment arms that they received) which could impact the safety analysis. This reviewer reanalyzed the data below, using the denominator as the planned safety analysis population and categorizing individual AEs with the treatment received at the time of the AE. The denominator is lower, as it included patients only once and based on their randomized treatment arm. The results were similar, and thus the Applicant's presented data will be shown elsewhere in this review.

Table 44: Medical Officer Overview of Adverse Events from Pooled Phase 2 and 3 Studies

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

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

Reviewer Comment: As previously stated, the Applicant's included patients who were misallocated treatment twice in the denominator (i.e., includes misallocated patients in both treatment arms that they received) which could impact the safety analysis. This reviewer reanalyzed the AE data for the pooled phase 2 and 3 studies in ***Table 44*** *above, using the denominator as the planned safety analysis population and categorizing individual AEs with the treatment received at the time of the AE. The denominator is lower, as it included patients only once and based on their randomized treatment arm. The results from the MO analysis were similar, and thus the Applicant's presented data will be shown elsewhere in this review, unless otherwise noted.*

7.3.1 Deaths

No patient died while participating in any study during the eluxadoline clinical development program, however, 1 patient death was reported during the conduct of Study IBS-3001.

> 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, from (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. One day 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 cite 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) (4) 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.

Reviewer comment: This reviewer agrees with the investigator's assessment that the single death which occurred during IBS-3001 was not 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.

7.3.2 Nonfatal Serious Adverse Events

A pooled summary of SAEs reported by more than 1 patient by SOC during Phase 2 and Phase 3 studies in the 75mg, 100mg, and placebo treatment arms is provided below. The proportion of patients with SAEs was slightly higher in patients receiving eluxadoline compared to placebo (4.2% 75mg, 4.0% 100mg, and 2.6% placebo). The

most commonly reported SAEs were within the gastrointestinal disorders SOC, and pancreatitis was the most commonly reported SAE with 11 reported cases. 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. Finally, 1 patient in IBS-3002 in the 100mg treatment arm had an SAE of ischemic colitis. These ischemic colitis and small bowel obstruction event which occurred in the eluxadoline treatment arm are briefly described below:

- **IBS-3001-083/0012:** A 59-year old female patient experienced an SAE of small bowel obstruction (b) (4) days after beginning therapy with eluxadoline 100mg BID. She had a history of a tubal ligation, and exploratory laparotomy showed an ileal stricture. She underwent 2 small bowel resections, discontinued from the trial, and recovered from the event. The event was assessed by the investigator as a small bowel obstruction secondary to ileal stricture and unlikely related to study drug.
- **IBS-3002-800/0004:** A 72-year old female patient experienced an SAE of ischemic colitis 19 days after beginning therapy with eluxadoline 100mg BID. She had multiple comorbidities, 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. She fully recovered and discontinued from the trial. The event was assessed by the investigator as unlikely related to study drug. This is further discussed in **7.3.5 Submission Specific Primary Safety Concerns**, below.

Table 45: Serious Adverse Events, Pooled Phase 2 and 3 Analysis

System Organ Class	Number (%) of Patients		
	Eluxadoline 75 mg BID (N = 807)	Eluxadoline 100 mg BID (N = 1032)	Placebo BID (N = 975)
Serious AEs	40	65	28
Number of patients with ≥ 1 SAE	34 (4.2)	41 (4.0)	25 (2.6)
Gastrointestinal disorders	8 (1.0)	13 (1.3)	4 (0.4)
Infections and infestations	9 (1.1)	4 (0.4)	4 (0.4)
Cardiac disorders	3 (0.4)	4 (0.4)	2 (0.2)
Injury, poisoning, and procedural complications	3 (0.4)	3 (0.3)	3 (0.3)
Musculoskeletal and connective tissue disorders	3 (0.4)	2 (0.2)	3 (0.3)
Nervous system disorders	4 (0.5)	3 (0.3)	1 (0.1)
Psychiatric disorders	2 (0.2)	3 (0.3)	2 (0.2)
General disorders and administrative site conditions	2 (0.2)	2 (0.2)	1 (0.1)
Vascular disorders	2 (0.2)	3 (0.3)	0
Investigations	1 (0.1)	3 (0.3)	0
Metabolism and nutrition disorders	0	2 (0.2)	2 (0.2)
Reproductive system and breast disorders	1 (0.1)	1 (0.1)	1 (0.1)
Respiratory, thoracic, and mediastinal disorders	0	2 (0.2)	1 (0.1)
Hepatobiliary disorders	0	2 (0.2)	0
Renal and urinary disorders	0	1 (0.1)	1 (0.1)
Eye disorders	0	0	1 (0.1)
Neoplasms benign, malignant, and unspecified	1 (0.1)	0	1 (0.1)
Pregnancy, puerperium, and perinatal conditions	1 (0.1)	0	0
Skin and subcutaneous tissue disorders	0	1 (0.1)	0

Source: Applicant ISS Amendment Table 2.71

In addition, there were 2 additional cases of pancreatitis in the 200mg BID group in Study IBS-2001.

Reviewer Comments: The overall rates of serious adverse events are low and the proportions were similar across treatment arms. Pancreatitis was the most commonly reported SAE in eluxadoline treated patients, and it is included in the Warnings and Precautions of the Prescribing Information. Pancreatitis is also documented in patients taking other opiates, and some cases are thought to be related to sphincter of Oddi spasm. Patients with a history of pancreatitis or alcohol abuse (at risk for pancreatitis) are contraindicated to eluxadoline. This reviewer feels this is appropriate. Small bowel obstruction occurred equally in patients in the eluxadoline and placebo arms. By patient narrative it appears both events were related to previous surgeries and were unrelated

to constipation. The single case of ischemic colitis occurred in an older patient with multiple comorbidities – while ischemic colitis has been associated with alosetron, the MOA of the two drugs is different, and the patient in IBS-3002 did not appear to experience any constipation. By history, the most plausible explanation was that a GI bleeding event (h/o diverticuli) led to hypotension and ischemic colitis. At this time, this reviewer does not believe inclusion of this SAE is warranted in the label. This reviewer believes it is difficult to draw any specific conclusions at this time, and routine postmarketing monitoring is appropriate.

7.3.3 Dropouts and/or Discontinuations

A total of 340 (34.5%) patients receiving eluxadoline 100mg BID discontinued from Phase 2 or 3 Studies, compared to 321 (32.7%) of patients receiving placebo. The most common reason for discontinuation was "voluntarily withdrew". More patients discontinued from eluxadoline treatment arms (8.4% 75mg, 8.0% 100mg) due to adverse events as compared to the placebo arm (4.3%).

Table 46: Disposition of Pooled Phase 2 and 3 Studies[a]

	Number (%) of patients		
	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo
Total Number of Patients			
Enrolled	810	985	981
Completed Study	507 (62.6)	644 (65.4)	660 (67.3)
Discontinued Study	303 (37.4)	340 (34.5)	321 (32.7)
Primary Reason for Discontinuation			
Voluntarily withdrew	164 (20.2)	155 (15.7)	178 (18.1)
Adverse event or SAE	68 (8.4)	79 (8.0)	42 (4.3)
Lost to follow-up	36 (4.4)	32 (3.2)	28 (2.9)
Sponsor decision	8 (1.0)	25 (2.5)	20 (2.0)
Physician decision	21 (2.6)	22 (2.2)	25 (2.5)
Lack of efficacy	3 (0.4)	16 (1.6)	18 (1.8)
Protocol violation	3 (0.4)	9 (0.9)	9 (0.9)
Diary-confirmed constipation	0	2 (0.2)	1 (0.1)

Source: Modified from Applicant ISS Amendment Table 2.1
[a] Only the 75mg BID, 100mg BID, and placebo treatment arms were included from Studies IBS-2001, IBS-3001, and IBS-3002

Adverse events most commonly resulting in discontinuation in patients taking eluxadoline were from the GI disorders SOC and included abdominal pain, constipation, and nausea. No other AE resulting in discontinuation was reported in > 0.6% of patients in the eluxadoline 75 or 100mg treatment arms. **Table 47** below shows adverse events leading to treatment discontinuations from the pooled Phase 2 and 3 Studies, including eluxadoline 75mg, 100mg, and 200mg compared with placebo.

Table 47: Adverse Events Leading to Treatment Discontinuation in ≥ 1 % of Patients – Pooled Phase 2 and 3 Studies

	Number (%) of patients			
	Eluxadoline 75 mg BID N = 807	Eluxadoline 100 mg BID N = 1032	Eluxadoline 200 mg BID N = 171	Placebo BID N = 975
Number of patients with ≥ 1 AE leading to discontinuation	67 (8.3)	80 (7.8)	22 (12.9)	42 (4.3)
Abdominal Pain[a]	12 (14.9)	15 (14.5)	12 (7.0)	3 (0.3)
Constipation	9 (1.1)	15 (1.5)	4 (2.3)	3 (0.3)
Nausea	5 (0.6)	0	4 (2.3)	4 (0.4)
Headache	3 (0.4)	1 (0.1)	3 (1.8)	1 (0.1)
Dizziness	1 (0.1)	1 (0.1)	3 (1.8)	2 (0.2)
Vomiting	1 (0.1)	2 (0.2)	2 (1.2)	1 (0.1)
Fatigue	0	0	2 (1.2)	2 (0.2)
Dry Mouth	0	0	3 (1.8)	0
Somnolence	0	1 (0.1)	2 (1.2)	0
Pruritis	1 (0.1)	0	2 (1.2)	0

Source: Applicant ISS Amendment Table 2.49
[a] Abdominal pain includes both AEs of abdominal pain and abdominal pain upper which resulted in study drug discontinuation

Reviewer Comments: The higher discontinuation rate in eluxadoline treatment arms for AEs of abdominal pain is somewhat concerning to this reviewer, given the treatment is intended to improve abdominal pain. This is not entirely inconsistent with the efficacy results, however, which seem to show that improvements in stool consistency are driving the results.

7.3.4 Significant Adverse Events

As shown in Section 7.3.3, there was a higher rate of discontinuation for AEs of abdominal pain in the eluxadoline treatment arms than placebo. **Table 48** below summarizes AEs of abdominal pain from Phase 2 and 3 studies by severity, categorization as serious, and whether they led to discontinuation, to determine if there was an imbalance in significant abdominal pain associated with eluxadoline treatment.

Table 48: Overall Summary of Adverse Events of Abdominal Pain, Pooled Phase 2 and 3 Analysis

	Number (%) of Patients		
AEs of Abdominal Pain	**Eluxadoline 75mg BID (N=807)**	**Eluxadoline 100mg BID (N=1032)**	**Placebo BID (N=975)**
Overall AEs of Abdominal Pain[a]	69	92	54
Leading to Discontinuation	12 (14.9)	15 (14.5)	2 (0.3)
Categorized as Serious[b]			
yes	3	3	0
no	66	89[b]	54
Categorized as Severe			
yes	4	13	6
no	65	79	48

[a] For the purposes of this analysis, this reviewer used a broad search of MedDRA terms for abdominal pain (abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness)
[b] Patients with more than one AE of abdominal pain categorized fitting into both serious and non-serious categories were listed only once as serious
[c] Patients with more than one AE of abdominal pain categorized with different severity were listed only once with their most severe AE of abdominal pain listed as severe or not severe

The Applicant also provided a summary of abdominal pain adverse events using a narrow search including only the preferred term of "abdominal pain" in the eluxadoline Phase 2 and 3 studies, including a breakdown of the time course of the initial reporting of symptoms as well as based on prior cholecystectomy status. The incidence of AEs of abdominal pain was higher in the eluxadoline treatment groups than the placebo group (4.1% 75mg, 4.6% 100mg, 2.6% placebo), however, the rates were similar when looking at events occurring after the first week of treatment. This is shown in **Table 49** below.

Table 49: Summary of Abdominal Pain Adverse Events from Pooled Phase 2 and 3 Studies

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

Source: Response to Agency Questions During 10Dec2014 Midcycle Communication Meeting, Received 12January2015
[a] This summary includes only AEs coded with the preferred term "abdominal pain"
[b] Incidence calculated as the difference of "Overall" – "Within first week" rows presented in Table 1. Percentage of patients is based on overall treatment group N.
[b] Prior cholecystectomy status was prospectively captured in Phase 3 studies only. AE summary by prior cholecystectomy status includes only Phase 3 patients, with N for patients with/without prior cholecystectomy status for each treatment group presented as the denominator within each cell.

In patients with prior cholecystectomy there was a higher incidence of AEs of abdominal pain in patients receiving eluxadoline 100mg (9.8%) compared to 75mg (4.8%) and placebo (3.8%). This reviewer asked the Applicant to provide the same analysis using a broader MedDRA search, and the results were similar. This is shown in **Table 50** below.

Table 50: Incidence of Abdominal Pain Adverse Events based on Cholecystectomy Status Using Broad MedDRA Search Term: Pooled Phase 2 and 3 Studies

	Eluxadoline 75mg BID	Eluxadoline 100mg BID	Placebo BID
Any AE of Abdominal Pain by Prior Cholecystectomy Status[b], n/N(%)			
Overall (prior cholecystectomy)	16 /165 (9.7)	29/183 (15.8)	15/158 (9.5)
Overall (no prior cholecystectomy)	52/642 (8.1)	49/676 (7.2)	31/650 (4.8)

[a] Abdominal Pain AE comprises abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, and abdominal distension

[b] Prior cholecystectomy status was prospectively captured in Phase 3 studies only. N for the denominator within each cell represents patients with and without prior cholecystectomy for each treatment group.

Reviewer Comments: Based on the Applicant's response to questions during the midcycle meeting summarized above, this reviewer agrees that there was a higher incidence of abdominal pain in the eluxadoline treatment groups early during the course of treatment, compared to placebo. When looking only at AEs of abdominal pain which occurred after week 2, the incidence was similar across treatment groups. Similarly, discontinuations due to abdominal pain AEs tended to occur early in the course of treatment and were similar across treatment groups after the first week. There appeared to be a slightly higher incidence of abdominal pain in patients receiving 100mg eluxadoline, and this was particularly evident in patients with a prior cholecystectomy (9.8% 100mg, 4.8% 75mg, and 3.8% placebo). The sponsor analyzed AEs of abdominal pain by cholecystectomy status using both a broad and narrow MedDRA search. In both cases, patients in the 100mg treatment arm had a significantly higher incidence of abdominal pain than patients in the 75mg treatment arm.

The Applicant proposes that most of these AEs of abdominal pain resembled AEs described as sphincter of Oddi spasm, however, associated laboratory data was not obtained and these events were unable to be adjudicated as such. This is a reasonable hypothesis, particularly given the higher incidence in patients with prior cholecystectomy. The Applicant proposes marketing the 75mg dose for patients who have had a prior cholecystectomy or who cannot tolerate the 100mg dose. Given the 75mg was demonstrated to be effective and there is the potential for increased abdominal pain with the 100mg dose, particularly in patients with prior cholecystectomy, this reviewer believes this is an acceptable approach.

7.3.5 Submission Specific Primary Safety Concerns

As described in Section 7.2.6, submission specific primary safety concerns included AEs related to sphincter of Oddi (SO) spasm, including pancreatitis and hepatobiliary events; constipation events, especially severe complications of constipation; events of

fall, syncope, and road traffic accidents, and special considerations related to abuse and withdrawal potential. Adverse events potentially related to ischemic colitis were also considered, as this is a potential AE associated with alosetron, the only approved treatment for IBS-D, and the mechanism for this ischemic colitis is not entirely understood.

Sphincter of Oddi Spasm:
In Studies IBS-2001, IBS-3001 and IBS-3002, 484 adverse events were identified that matched a pre-specified MedDRA term as possibly related to SOD. Of these 484 events:

- 447 did not meet the criteria for adjudication
  - 376 did not result in study drug withdrawal
  - 47 did not have laboratory or diagnostic testing
  - 24 did not meet criteria for various other reasons
- 37 suspected events were submitted to the committee for adjudication

Of these 37 suspected cases, 9 cases were adjudicated as having pancreatitis and 9 cases were adjudicated as having acute biliary events. All patients who were adjudicated had received treatment with eluxadoline. **Table 51** and **Table 52** provide summaries of pancreatitis and hepatobiliary events from pooled Phase 2 and 3 studies, including all doses.

Table 51: Summary of Pancreatitis Cases from Pooled Phase 2 and 3 Studies

	n	Prior Cholecystectomy, n (% of cases)
Total pancreatitis cases in ISS database	11	6 (55%)
Cases adjudicated as pancreatitis[a]	9	4 (44%)
Cases on eluxadoline at time of onset of pancreatitis	8	4 (50%)
Cases adjudicated as consistent with SO Spasm	3	3 (100%)
Cases associated with EtOH	4	1 (25%)
Cases associated with biliary sludge	1	0 (0%)

Source: Applicant ISS Table 9-10
[a] Potential cases of pancreatitis were adjudicated by the HPAC using the Atlanta Criteria for pancreatitis. 2 patients failed to meet the Atlanta criteria. Patient 112/0006 experienced abdominal pain with lipase <2X ULN and demonstrated a normal pancreas on CT scan. This patient had a h/o cholecystectomy and was classified as SO spasm but not meeting the criteria for pancreatitis. Patient 145/0004 did not have clinical features, chemistry, or imaging data to support the diagnosis of pancreatitis.

Of 9 patients adjudicated as pancreatitis by the Atlanta Criteria, 3 cases were adjudicated as consistent with SO spasm. All of these patients experienced symptoms during the first day of treatment, were briefly hospitalized, discontinued study drug and had complete resolution of symptoms.

- **IBS2001-074/0001:** 29-year old obese diabetic female s/p cholecystectomy presented with abdominal pain, nausea, and vomiting with increased pancreatic enzymes within several hours of receiving first eluxadoline dose. Patient's symptoms and labs resolved rapidly with discontinuation.
- **IBS2001-277/0001:** 51-year old female smoker s/p cholecystectomy with recent alcoholic pancreatitis prior to study presented with abdominal pain, elevated blood alcohol, and increased lipase after 2 doses of study drug.
- **IBS2001-144/0003:** 62-year old female s/p cholecystectomy experienced mild symptoms of pancreatitis with normal CT minutes after first dose of eluxadoline. Patient's symptoms and labs resolved rapidly with discontinuation.

Of the 6 patients not adjudicated as consistent with SO spasm:

- **IBS2001-047/0003:** 18-year old female who developed pancreatitis 15 days after discontinuing treatment. She was receiving antibiotics associated with pancreatitis (clarithromycin). Lipase was normal after 1 day.
- **IBS2001–125/001:** 63-year old male with longstanding severe alcoholism and prior pancreatitis and imaging studies showing hepatic steatosis or steatohepatitis. He reported significant alcohol consumption in the days preceding his event. He improved clinically in 1 – 2 days, however his enzymes took several weeks to normalize.
- **IBS3002-712/0005:** 50-year old female with h/o regular consumption of vodka presented with pancreatitis after 4 weeks of therapy. Prior biopsy showed steatohepatitis.
- **IBS3002-677/0013:** 56-year old male with increased alcohol consumption, recent steroids, and opiates for back pain developed pancreatitis after approximately 10 weeks of therapy. Imaging studies showed hepatic steatosis, reflecting possible chronic alcohol use.
- **IBS2001-194/0002**: 28-year old female presented with pain and increased lipase after 18 days on study drug. She was not hospitalized and had no acute pancreatic findings on CT. She admitted to heavy drinking the day before the event and has had similar symptoms associated with heavy drinking in the past.
- **IBS3001-292/0001:** 43-year old obese female who presented after 26 weeks of study drug with an MRI showing biliary sludge/thickened bile.

Table 52: Summary of Acute Hepatobiliary Events from Pooled Phase 2 and 3 Studies

Cases adjudicated as acute hepatobiliary events	9
Cases adjudicated as consistent with SO spasm	9
Cases with absent gall bladder	8
Cases with unknown gall bladder anatomy[a]	1

Source: Applicant ISS Table 9 – 11

[a] Patient from IBS-2001, where cholecystectomy status was not prospectively collected

All 9 patients identified as having acute hepatobiliary events were adjudicated as SO spasm. All of these events were transient and resolved rapidly on discontinuation of therapy. Seven of the nine patients experienced onset of symptoms within the first week of treatment. Eight of 9 patients were managed as outpatients and 1 was hospitalized for control for nausea and vomiting. Two patients continued or resumed treatment after experiencing symptoms.

Table 53 below summarizes the rates of adjudicated hepatobiliary and pancreatic events, both throughout the entire eluxadoline clinical development program and considering only Phase 3 studies, as presented by the Applicant.

Table 53: Rates of Adjudicated Hepatobiliary and Pancreatic Events in Oral Eluxadoline Exposed Subjects

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

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

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

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

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

Reviewer Comments: The Applicant did a thorough job of identifying and adjudicating hepatobiliary and pancreatic events during Phase 3 studies. In addition, the adjudication committee was provided with 5 unblinded suspected cases of pancreatitis or acute hepatobiliary events from Study IBS-2001 which are included above (MedDRA coded as pancreatitis or hepatobiliary). No additional cases were identified in Phase 1 studies by this reviewer, on review of the ISS dataset.

SOD is a known class effect with opiate use, and it often occurs early in the treatment course. The incidence of SOD in patients receiving mu agonist, however, is not well described in the literature. The Sponsor currently proposes eluxadoline be contraindicated in patients with a history of pancreatitis, alcoholism, alcohol abuse, or alcohol addiction, or structural disease of the pancreas, known or suspected biliary or pancreatic tract obstruction, or sphincter of Oddi disease or dysfunction. This

information is also included in Warnings and Precautions, Section 5.1 Sphincter of Oddi Spasm, Pancreatitis, (b) (4) *. In review of the label of several mu agonists (codeine, tapentadol), SOD is described in the W&P section, though the use of the products in certain at risk populations is not a contraindication. The rate of SOD with eluxadoline appears consistent with that of other opiates, and this reviewer believes that placement of issues related to SOD is appropriate for W&P but not an absolute contraindication.*

The risk of SOD in patients s/p cholecystectomy receiving opiates has also been described in the literature. The risk for SOD in patients s/p cholecystectomy receiving eluxadoline does not appear to be greater than the risk associated with other opiates.

Serious Gastrointestinal Adverse Reactions, Including Serious Complications of Constipation and Ischemic Colitis:

Alosetron is a selective serotonin 5-HT_3 antagonist indicated for women with severe diarrhea-predominant irritable bowel syndrome. Alosetron is marketed under a REMS including restricted distribution, due to infrequent but serious gastrointestinal adverse reactions reported with its use. These events include ischemic colitis and serious complications of constipation, which have resulted in hospitalization, blood transfusion, surgery, and death. Eluxadoline is a mixed mu opioid receptor agonist/ delta opioid receptor antagonist with a different mechanism of action. However, given the potential risk associated with the only currently approved therapy for IBS-D, eluxadoline data was analyzed to determine if there was an increased risk for serious gastrointestinal adverse reactions with its use.

The rates of spontaneous reports of constipation were similar between the 75mg and 100mg groups (7.4% and 8.1%, respectively) and greater than that of placebo patients (2.5%). The Applicant reports no serious complications of constipation (e.g., hospitalization, surgery) during the eluxadoline clinical development program. There were 2 SAEs of small bowel obstruction which occurred during **Study IBS-3001**, 1patient in the placebo group and 1 patient in the eluxadoline 100mg treatment group. ISS – page 104. Patient 083/0012 had a history of tubal ligation 30 years prior to randomization. In the first 6 months of therapy, her diary demonstrated only 1 day of no bowel movement and no AEs of constipation or diary-confirmed constipation. She was on treatment for (b) (6) days when she was admitted to the hospital for an SAE of small bowel obstruction secondary to ileal stricture. She subsequently underwent two small bowel resections. **Table 54** provides a pooled summary of constipation AEs by quarter for patients receiving 75mg, 100mg, or placebo during Phase 2 or 3 studies.

Table 54: Summary of Constipation AEs by Quarter[a] – Pooled Phase 2 and 3 Studies

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

Source: Modified from Applicant ISS Amendment Table 2.68

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

One hundred sixty-four (164) patients in the eluxadoline 75mg, eluxadoline 100mg, and placebo treatment arms experienced 188 events of constipation during Phase 2 and 3 studies. None of these AEs were serious. **Table 55** below summarizes the AEs of constipation by severity for Phase 2 and 3 studies.

Table 55: Constipation AEs by Severity

	Number (%) of Patients		
Constipation AEs by Severity	Eluxadoline 75mg BID (N=807)	Eluxadoline 100mg BID (N=1032)	Placebo BID (N=975)
Mild	40 (5.0)	57 (5.5)	20 (2.1)
Moderate	20 (2.5)	31 (3.0)	9 (0.9)
Severe	4 (0.5)	7 (0.7)	0 (0)

Source: Created by Reviewer using ISS ADAE dataset

Constipation was also assessed using data from the IVRS diary entries. For these analyses, diary confirmed constipation was defined in two ways:

- The absence of bowel movement on at least 4 consecutive days based on non-missing IVRS diary entries
- Average weekly BSS scores < 2

A summary of IVRS (diary) confirmed constipation based on both definitions is included below for the first 3 quarters for patients in Phase 2 and 3 studies.

Table 56: Pooled Analysis of Phase 2 and 3 Studies: IVRS-Confirmed Constipation by Quarter[b]

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

Source: Applicant's ISS Amendment Tables 2.69 and 2.70
[a] Percentages are based on available diary data at each time point.
[b] A quarter is defined as a 13 week period, starting from date of first dose of study drug. IVRS was only completed through the end of Week 26 for both studies, so no data is available for IVRS confirmed constipation for Quarter 4.
[c] IVRS-confirmed constipation based on number of bowel movements is defined as the absence of a bowel movement on at least 4 consecutive days, based on non-missing IVRS diary entries.
[d] IVRS-confirmed constipation based on BSS score is defined as a weekly average BSS score of <2 over any study quarter based on the IVRS diary entries
[e] Quarter 3 IVRS entries comprises only patients in the single-blind withdrawal phase of Study IBS-3002 and patients in Study IBS-3001 who attended their Week 26 visit after Day 182.
n is the number of subjects with one or more events in the quarter, N' is the number of events.

Ischemic colitis: One case of ischemic colitis was reported during the eluxadoline clinical development program.

- IBS3002-800/0004: 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 14Mar2013. On [redacted] (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.

In an attempt to assess for a possible increased risk of ischemic colitis associated with eluxadoline, the ISS dataset for phase 2 and phase 3 studies was reviewed to determine if there was an imbalance in the number of patients reporting AEs consistent with rectal bleeding. Nineteen patients had 20 adverse events of rectal hemorrhage or hematochezia with more patients experiencing such events in the placebo arm than in the active treatment groups, as shown in **Table 57** below. Only 1 event of rectal bleeding was classified as severe, and this was in the placebo arm.

Table 57: Events of Rectal Bleeding in Phase 2 and 3 Studies

	Number (%) of Patients		
AEDECOD	**Eluxadoline 75mg BID (N=807)**	**Eluxadoline 100mg BID (N=1032)**	**Placebo BID (N=975)**
Hematochezia	0	1	2
Rectal Hemorrhage	5	6	7

Source: Created by Reviewer from ISS dataset

Reviewer Comments: Constipation occurred more frequently in the eluxadoline treatment groups. This is expected given the drug's mechanism of action. Importantly, none of these AEs of constipation were SAEs, and they were generally mild in severity. Eleven patients receiving eluxadoline assessed their constipation as severe (4 in 75mg and 7 in 100mg), however, compared to zero patients receiving placebo. Adverse events of constipation tended to occur early in treatment (Quarter 1). There were 2 cases of small bowel obstruction reported, 1 in a patient receiving 100mg eluxadoline and 1 in a patient receiving placebo, both from Study IBS-3001. The case in the 100mg group appeared related to an ileal stricture secondary to a prior tubal ligation. Given

there was also a single case in the placebo arm, this reviewer does not believe there is any indication that eluxadoline contributes to small bowel obstruction.

There was a single case of ischemic colitis reported during the eluxadoline clinical development program. This case occurred in a 72-year old female patient with multiple comorbidities. The event was assessed as unlikely related to drug. The patient was at high risk for gastrointestinal bleeding due to 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. In addition, diary data showed no evidence of constipation leading up to the event. Finally, while there is believed to be an increased risk for ischemic colitis with alosetron, the only approved therapy for IBS-D, eluxadoline is a different mechanism of action, and there is no known association between other opiates and ischemic colitis. This reviewer agrees that this SAE was unlikely related to study drug.

At this time, it appears that eluxadoline increases the risk of constipation, however, there is no evidence to indicate that eluxadoline increases the risk of serious complications of constipation or ischemic colitis.

Events of fall, syncope, and road traffic accidents:
The Applicant reported that adverse events of fall were reported in 1.6%, 0.9%, and 0.4% of patients across the 75mg, 100mg, and placebo groups, respectively, in the Phase 3 studies. There were no AEs of fall in the Phase 2 study. Syncope was reported for 0.2%, 0.3%, and 0.2% of patients in the 75mg, 100mg, and placebo groups, respectively. Ten patients had AEs of road traffic accidents who were driving during the Phase 3 studies. These were reported in 4 patients in the 75mg group, 2 patients in the 100mg group, and 2 patients in the placebo group.

Reviewer Comments: This reviewer separately queried the ISS dataset for AETERMs which could indicate a fall and results were similar to those described by the Applicant. The narratives for the traffic accidents were reviewed, and the majority of the accidents clearly show the other vehicle at fault. No driver's reported any CNS related AEs or other AEs which may have impaired their driving. The numbers for these AEs are small and it is difficult to draw any definitive conclusions, but there is insufficient data to suggest that eluxadoline has an impact on events of fall, syncope, and road traffic accidents.

AEs Suggesting Abuse Potential:
The Applicant assessed for AEs suggesting abuse potential using a list of MedDRA terms derived from the FDA Draft Guidance for Industry, Assessment of Abuse Potential of Drugs, a 2008 public presentation by FDA Controlled Substance Staff, and input from key opinion leaders. The overall incidence of AEs potentially related to abuse was similar across treatment arms (7.9% 75mg, 9.6% 100mg, and 8.1% placebo). The most

common AEs potentially related to abuse were dizziness and fatigue which both had similar incidence across treatment groups.
Table 58 below is a summary of these AEs, including only PTs which occurred in > 1.0 % of patients in any of the included treatment groups (75mg, 100mg, placebo). In addition to the AEs listed below, AE of euphoric mood was reported by 2 patients in the pooled Phase 2 and 3 safety set, both of these patients received eluxadoline 100mg BID (0.1%).

		Number (%) of Patients	
AEs of Abdominal Pain	**Eluxadoline 75mg BID (N=807)**	**Eluxadoline 100mg BID (N=1032)**	**Placebo BID (N=975)**
Abuse potential related AEs	88	124	98
Number of patients with ≥ 1 abuse potential related AE	64 (7.9)	99 (9.6)	79 (8.1)
Dizziness	21 (2.6)	33 (2.6)	21 (2.2)
Fatigue	21 (2.6)	20 (1.9)	23 (2.4)
Anxiety	10 (1.2)	20 (1.9)	17 (1.7)
Depression	9 (1.1)	12 (1.2)	11 (1.1)
Somnolence	1 (0.1)	11 (1.1)	3 (0.3)

Table 58: Adverse Events Potentially Related to Abuse – Pooled Phase 2 and 3

		Number (%) of Patients	
AEs of Abdominal Pain	**Eluxadoline 75mg BID (N=807)**	**Eluxadoline 100mg BID (N=1032)**	**Placebo BID (N=975)**
Abuse potential related AEs	88	124	98
Number of patients with ≥ 1 abuse potential related AE	64 (7.9)	99 (9.6)	79 (8.1)
Dizziness	21 (2.6)	33 (2.6)	21 (2.2)
Fatigue	21 (2.6)	20 (1.9)	23 (2.4)
Anxiety	10 (1.2)	20 (1.9)	17 (1.7)
Depression	9 (1.1)	12 (1.2)	11 (1.1)
Somnolence	1 (0.1)	11 (1.1)	3 (0.3)

Source: Applicant ISS Table 12-8
Other PTs included in the applicant's search for potential abuse related AEs were hypoesthesia, paresthesia, asthenia, lethargy, nervousness, sedation, abnormal dreams, euphoric mood, feeling drunk, restlessness, affective disorder, agitation, depressed mood, disturbance in attention, emotional distress, energy increased, memory impairment, mood swings, and nightmare

Reviewer Comment: no data to suggest an imbalance in AEs potentially related to abuse.

Special considerations related to abuse and withdrawal potential are also discussed in Section 7.4.5.

Withdrawal Potential:
The subjective opiate withdrawal scale (SOWS) was used in Phase 3 studies to screen for potential withdrawal effects. This is described in Section 7.2.6 above. Patients in IBS-3001 completed the SOWS at Week 52 or at early withdrawal. Patients in IBS-3002 completed the SOWS only for patients who discontinued from the study prior to completion of the double blind treatment period at Week 26. This was in order to not jeopardize the 4-week single-blind placebo washout. Descriptive statistics for SOWS results from the pooled Phase 3 studies is provided in **Table 59** below.

Table 59: Summary of SOWS Results from Pooled Phase 3 Studies

SOWS total score	Eluxadoline 75mg BID (N=807)	Eluxadoline 100mg BID (N=1032)	Placebo BID (N=975)
Overall			
n	422	424	422
Mean (SD)	5.9 (8.56)	6.0 (8.46)	6.4 (8.76)
Median	2.0	3.0	3.0
Min, Max	0, 54	0, 56	0, 56
0 days post-treatment			
n	86	94	91
Mean (SD)	4.5 (6.17)	4.7 (6.99)	6.5 (9.05)
Median	1.5	1.0	3.0
Min, Max	0, 22	0, 28	0, 42
1 day post-treatment			
n	196	196	202
Mean (SD)	5.5 (8.75)	5.5 (7.67)	5.9 (8.11)
Median	2.0	3.0	3.0
Min, Max	0, 48	0, 47	0, 56
2 days post-treatment			
n	8	10	11
Mean (SD)	7.9 (7.43)	4.9 (6.12)	5.7 (4.98)
Median	8.0	4.0	6.0
Min, Max	0, 22	0, 20	0, 15
3 days post-treatment			
n	4	8	6
Mean (SD)	10.0 (11.52)	4.3 (5.09)	4.7 (5.68)
Median	7.5	2.5	3.0
Min, Max	0, 25	0, 14	0, 16
> 3 days post-treatment			
n	118	106	105
Mean (SD)	6.9 (9.43)	8.0 (11.04)	7.4 (10.04)
Median	3.0	4.0	4.0
Min, Max	0, 54	0, 56	0, 52

Source: Applicant ISS Amendment Table 2.86

The Applicant also analyzed AEs which occurred during the 2-week post-treatment follow-up period for Study IBS-3001 and during the 4-week single-blind withdrawal period of Study IBS-3002. In Study IBS-3001, 783 patients completed the double-blind treatment period and were assessed during the 2-week follow-up. A total of 52 patients (4.1%) had at least 1 AE during the post-treatment period, and the incidence was similar across treatment groups (4.0% 75mg, 4.2% 100mg, and 4.0% placebo). The AEs of the gastrointestinal disorders SOC (abdominal pain, constipation, diarrhea) occurred in

more than 1% of patients during the follow-up period, and these at a similar rate across treatment arms (0.9% 75mg, 1.2% 100mg, 1.2% placebo). A summary of adverse events occurring following the double-blind treatment in IBS-3001 is shown in **Table 60** below.

Table 60: Summary of Adverse Events During 2-Week Follow-Up Period, IBS-3001

	Eluxadoline 75mg BID (N = 426)	Eluxadoline 100mg BID (N = 424)	Placebo BID N = 426	Total N = 1276
Total patients completing double-blind period	257	257	269	783
Total number of follow-up period adverse events	24	21	20	65
Number of patients with at least one follow-up period adverse event	17 (4.0%)	18 (4.2%)	17 (4.0%)	52 (4.1%)
Gastrointestinal Disorders	4 (0.9%)	5 (1.2%)	5 (1.2%)	14 (1.1%)

Source: Applicant Clinical Study Report, Study IBS-3001, Table 14.3.1.9

In Study IBS-3002, 771 patients received placebo during the 4-week single-blind withdrawal period. Twenty-five of these patients who were misallocated active treatment during the 4-week single-blind withdrawal were not included in the withdrawal assessment. A total of 67 patients (5.9%) had at least 1 AE during the post-treatment period, and the incidence was similar across treatment groups (5.8% 75mg, 6.1% 100mg, and 5.8% placebo). The only AEs occurring in more than 2 patients were headache (n = 4), sinusitis (n = 3), upper respiratory tract infection (n = 3), ALT increased (n = 3), and arthralgia (n = 3). These AEs were generally distributed across all treatment groups.

Reviewer Comment: The total SOWS score ranges from 0 to 64. It has been suggested that (summed) scores below the mid-teens generally reflect minimal or mild withdrawal discomfort, scores in the high-teens and low thirties generally reflect moderate withdrawal discomfort, and higher scores reflect severe withdrawal. The SOWS scores recorded during Phase 3 Studies were very low (~5), and this reviewer does not believe there is any evidence of withdrawal potential. Patients from Study IBS-3002 who completed the study and single blind withdrawal did not complete the SOWS. The Applicant states this was in order to preserve the blind for this portion of the study, however, this was unfortunate, as this information would have been informative. The AE data from the 2-week post-treatment period for IBS-3001 and the 4-week single-blind withdrawal period for IBS-3002 show no indication of symptoms related to withdrawal.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most commonly reported adverse events during phase 2 and 3 Studies of eluxadoline were within the GI disorders and infections and infestations SOCs. In general, the rates of common adverse events were similar across treatment groups, with the exception of AEs of the GI SOC, which were reported more frequently in the eluxadoline treatment arms (30.0% and 26.5%) compared to placebo (19.0%). The frequency of AEs occurring in at least 2% of patients receiving eluxadoline 75mg or 100mg and occurring more frequently than in placebo, are summarized in **Table 61** below.

Table 61: Adverse Events Reported by ≥2% of Patients in either 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 75 mg BID (N = 807)	Eluxadoline 100 mg BID (N = 1032)	Placebo BID (N = 975)
Total number of AEs	1556	1804	1573
Number of patients with ≥ 1 AE	486 (60.2)	575 (55.7)	533 (54.7)
Gastrointestinal disorders	**242 (30.0)**	**273 (26.5)**	**185 (19.0)**
Nausea	65 (8.1)	73 (7.1)	49 (5.0)
Constipation	60 (7.4)	84 (8.1)	24 (2.5)
Abdominal pain	33 (4.1)	47 (4.6)	25 (2.6)
Vomiting	32 (4.0)	43 (4.2)	12 (1.2)
Flatulence	21 (2.6)	33 (3.2)	17 (1.7)
Abdominal Distension	21 (2.6)	28 (2.7)	15 (1.5)
Infections and infestations	**199 (24.7)**	**222 (21.5)**	**230 (23.6)**
Upper respiratory tract infection	27 (3.3)	53 (5.1)	38 (3.9)
Nasopharyngitis	33 (4.1)	31 (3.0)	33 (3.4)
Sinusitis	27 (3.3)	27 (2.6)	35 (3.6)
Bronchitis	26 (3.2)	30 (2.9)	21 (2.2)
Gastroenteritis viral	22 (2.7)	14 (1.4)	18 (1.8)
Urinary tract infection	17 (2.1)	18 (1.7)	21 (2.2)
Nervous system disorders	**81 (10.0)**	**112 (10.9)**	**99 (10.2)**
Headache	32 (4.0)	44 (4.3)	44 (4.5)
Dizziness	21 (2.6)	33 (3.2)	21 (2.2)
General disorders and administrative site conditions	**47 (5.8)**	**64 (6.2)**	**65 (6.7)**
Fatigue	21 (2.6)	20 (1.9)	23 (2.4)
Investigations	**77 (9.5)**	**70 (6.8)**	**78 (8.0)**
ALT increased	17 (2.1)	26 (2.5)	14 (1.4)
Vascular disorders	**25 (3.1)**	**25 (2.4)**	**25 (2.6)**
Hypertension	20 (2.5)	14 (1.4)	16 (1.6)

Source: Applicant ISS Amendment Table 2.29.
Note: For the SOC and preferred term level summaries, multiple occurrences a SOC or preferred term within a patient are counted only once.

Reviewer Comments: AEs were most commonly reported in the GI disorders SOC, and there was a higher proportion of patients in the eluxadoline treatment arms with AEs in this SOC. AEs in all other SOCs occurred in similar proportions across treatment groups. AEs of abdominal pain and constipation are discussed in greater detail in Sections 7.3.4 and 7.3.5.

7.4.2 Laboratory Findings

There were no treatment related trends in mean serum chemistry or hematology results over time – the mean values observed at the end of treatment were similar to those observed at baseline in each treatment arm. Specific laboratory assessments are discussed in more detail below.

ALT: The incidence of patients with post-randomization ALT elevations > 3xULN was similar between the eluxadoline treatment arms and placebo (3.2% 75mg, 2.1% 100mg, 2.1% placebo). The incidence of patients with ALT values >3xULN was slightly higher in patients who had a cholecystectomy prior to study enrollment (26 of 348 [7.5%] patients receiving eluxadoline and 9 of 159 [5.7%] patients for placebo). Five patients in Phase 2 and 3 studies had an ALT of > 10xULN to 20xULN, however, 3 of these patients were adjudicated as having SO spasm. Of the remaining 2 patients, sampling error at the site was suspected in one patient receiving 100mg eluxadoline in Study IBS-3001, and a patient receiving eluxadoline 200mg had an ALT value of 615 U/L and was diagnosed with acute hepatitis B infection. **Table 62** below summarizes post-randomization increases in ALT in the Safety Analysis Set from Phase 2 and 3 Studies.

Table 62: Post-Randomization Increase in ALT from Pooled Phase 2 and 3 Safety Analysis Set

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

Source: Applicant Integrated Summary of Safety, Table 10-1
[a] Patients were eligible for study entry with ALT up to 3xULN.

Bilirubin: The incidence of total bilirubin elevations >1.5ULN was low and similar across treatment arms (1.9% 75mg, 1.3% 100mg, and 1.2% placebo).

Alkaline Phosphatase: The incidence of alkaline phosphatase elevations >1.5ULN was low and similar across treatment arms (0.9% 75mg, 0.8% 100mg, 0.4% placebo).

No patient had an elevation of ALT ≥3xULN accompanied by a total bilirubin of ≥2xULN in the pooled Phase 2 and 3 safety population.

Reviewer Comments: There were no cases of Hy's Law in the eluxadoline clinical development program. This reviewer believes that excluding lab abnormalities associated with SO spasm, there is no evidence of clinically meaningful changes in laboratory findings associated with eluxadoline use.

7.4.3 Vital Signs

No clinically important treatment differences in the mean change in vital signs were observed between treatment groups in the Phase 2 and 3 studies.

In the first-in-human dose-escalation study (Study EDI-1001) and the initial food effect study, there was an increased incidence of orthostatic hypotension in subjects administered ≥500mg of eluxadoline compared with placebo. As a result, extensive blood pressure monitoring was implemented for Study IBS-2001, including ambulatory blood pressure monitoring in a subset of patients. In 41 patients who participated in ambulatory blood pressure monitoring, mean ambulatory blood pressure values were similar between treatment groups (eluxadoline 5, 25, 100, and 200mg BID) and were similar to those observed at baseline. In addition, patients were assessed for orthostatic blood pressure at Day 1 and Weeks 2, 4, and 8 by assessing BP after the patient had been sitting for 5 minutes and then repeating immediately after the patient stood up. A patient was defined as having "orthostatic hypotension" if he or she experienced a 20mm decrease in systolic blood pressure or a 10mm decrease in diastolic blood pressure between sitting and standing measurements. The incidence of orthostatic blood pressure with this definition was similar across treatment groups at every assessment time period, as shown in **Table 63** below.

Table 63: Orthostatic Hypotension in Study IBS-2001

	Number (%) of Patients				
Patients with Orthostatic Hypotension	Eluxadoline 5 mg BID N = 105	Eluxadoline 25 mg BID N = 170	Eluxadoline 100 mg BID N = 165	Eluxadoline 200 mg BID N = 172	Placebo BID N = 159
Day 1	14 (13.3)	19 (11.2)	21 (12.8)	22 (12.9)	16 (10.1)
Week 2	4 (4.2)	6 (3.8)	8 (5.6)	2 (1.4)	5 (3.4)
Week 4	4 (4.4)	4 (2.8)	3 (2.2)	5 (3.8)	5 (3.6)
Week 8	1 (1.5)	4 (2.9)	4 (3.1)	4 (3.5)	4 (3.3)

Source: Study IBS-2001 CSR Table 14.3.3.3

Reviewer Comments: This reviewer believes there is no evidence of clinically meaningful changes in blood pressure, including orthostatic hypotension with eluxadoline at the proposed marketed doses.

7.4.4 Electrocardiograms (ECGs)

ECG measurements were similar across treatment groups with no clinically significant changes from baseline observed. Adverse events of prolonged QT interval occurred in 1 patient each in the 25mg and 75mg groups, 3 patients in the 100mg group, and 3 patients in the placebo group. Three patients in the placebo group showed ECG signs of myocardial ischemia, and abnormal ST segment, abnormal T wave, and T wave inversion occurred in 1 patient each in the 100mg group and the placebo group. In addition, a thorough QTc study showed that single doses of eluxadoline 100mg and 1000mg to healthy subjects did not have significant effects on cardiac repolarization.

Reviewer Comments: This reviewer agrees there was no evidence of ECG changes with eluxadoline treatment.

7.4.5 Special Safety Studies/Clinical Trials

Clinical Trials to assess the oral abuse potential of eluxadoline are described in **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**, below.

7.4.6 Immunogenicity

No specific studies have been performed to determine the immunogenicity of eluxadoline, as eluxadoline is not a therapeutic protein product.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The adverse event rates were similar between dosing groups, when looking at the data from pooled Phase 2 and 3 Studies. Specifically, 54.7% of patients in placebo arms from Phase 2 and 3 studies experienced one or more AE, compared to 55.7% in the 100mg BID group and 60.2% in the 75mg BID group. There appeared to be a slightly higher incidence of abdominal pain in patients receiving 100mg eluxadoline, compared to the 75mg dose and placebo, and this was particularly evident in patients with a prior cholecystectomy (9.8% 100mg, 4.8% 75mg, and 3.8% placebo).
See also Section **7.2.2 Explorations for Dose Response** and **7.3.4 Significant Adverse Events**.

Reviewer Comments: there were no clear dose-dependent AEs, however, there was a suggestion for increased AEs of abdominal pain in the higher dose group. The Applicant proposes these AEs were likely non-adjudicated mild cases of SO spasm,

given they tended to occur more commonly early in the course of treatment and were most common in patients without a gallbladder. This is a reasonable assessment. Given the 75mg dose is shown to be effective, we recommend marketing both doses. The 75mg dose should be available to those who may not be able to tolerate the 100mg BID dose, due to abdominal pain, as well as patients who are s/p cholecystectomy and are at higher risk of SOD. This was discussed and agreed upon with the Applicant during the Mid-Cycle meeting.

7.5.2 Time Dependency for Adverse Events

When looking at AE rates by duration of eluxadoline exposure, no increased frequency was seen with longer periods of use. Adverse events in the GI SOC appeared to occur more frequently early in the course of therapy. Specifically, AEs of constipation occurred more frequently in the first Quarter for eluxadoline 75mg and 100mg (6.6% and 6.2%) and placebo (2.1%). Rates of AEs of constipation decreased significantly by Quarter 2 (1.4% 75mg, 1.9% 100mg, and 0.3% placebo). AEs of abdominal pain were reported more frequently within the first 2 weeks of treatment, compared with subsequent weeks in the treatment phase. See also **7.3.4 Significant Adverse Events** and **7.3.5 Submission Specific Primary Safety Concerns**.

Reviewer Comments: The Applicant describes the higher rate of AEs of constipation and abdominal early in the course of treatment in the full prescribing information. This is acceptable to this reviewer.

7.5.3 Drug-Demographic Interactions

No formal drug-demographic studies were conducted in support of this NDA, however, the Applicant analyzed the pooled safety data by gender, age, race, and body mass index.

Gender:
Across the pooled Phase 2 and 3 studies, 1068 (33.0%) patients were male and 2167 (67.0%) patients were female. Overall, a higher proportion of female patients reported AEs than male patients (60.0% vs 49.3%, respectively), and more female patients reported AEs of GI disorders (27.3% vs 20.8%). In addition, more females reported AEs of infections and infestations (24.8% vs 17.7%). Otherwise, the proportions of males and females with AEs by SOC were comparable. The proportion of SAEs were similar (2.3% vs 3.9%, respectively) across genders. The pattern of AE reporting was similar when looking at males and females separately, as compared with the full safety population. For example, the most commonly reported AEs among male and female patients were in the GI disorders SOC and included nausea, constipation, and abdominal pain. This is consistent with the findings from the full safety set. A pooled summary is provided in **Table 64** below.

Table 64: Overview of Adverse Events by Gender – Pooled Phase 2 and 3 Studies

	Number (%) of Patients		
	Eluxadoline 75mg BID	Eluxadoline 100mg BID	Placebo BID
Male, n	270	343	333
Adverse events	139 (51.5)	177 (51.6)	156 (46.8)
Serious adverse events	11 (4.1)	6 (1.7)	5 (1.5)
AEs leading to discontinuation	18 (6.7)	14 (4.1)	11 (3.3)
GI AEs	61 (22.6)	78 (22.7)	52 (15.6)
GI SAES	2 (0.7)	2 (0.6)	1 (0.3)
Female, n	537	689	642
Adverse events	347 (64.6)	398 (57.8)	377 (58.7)
Serious adverse events	23 (4.3)	35 (5.1)	20 (3.1)
AEs leading to discontinuation	49 (9.1)	66 (9.6)	31 (4.8)
GI AEs	181 (33.7)	195 (28.3)	133 (20.7)
GI SAES	6 (1.1)	11 (1.6)	3 (0.5)

Source: Applicant's Integrated Summary of Safety Amendment, Tables 2.22, 2.35, 2.55, and 2.77

Age:
Across the pooled Phase 2 and 3 studies, 1989 (92.4%) patients were <65 years of age and 246 (7.6%) patients were ≥65 years of age. Overall, a higher proportion of older patients reported AEs than younger patients (66.7% vs 55.6%). In addition, higher proportions of older patients than younger patients reported SAEs (7.0% vs 3.0%), AEs leading to discontinuation (11.9% vs 6.4%), GI AEs (34.2% vs 24.4%), and serious GI AEs (1.2% vs 0.9%). The pattern of AE reporting was similar across age groups. The most commonly reported AEs for both age groups was in the GI disorders SOC and included nausea, constipation, and abdominal pain. This is consistent with the findings from the full safety set.

Race and BMI:
AE rates were similar when analyzed across rates, as were SAE rates and AE rates leading to discontinuation. Similarly, BMI did not appear to impact the incidence or types of AEs reported.

Reviewer Comments: AEs in general, and GI AEs specifically, were reported by higher proportions of female patients than male patients. Similarly, AEs of all types were reported by higher proportions of older patients, compared with younger patients. The types of AEs reported were similar across demographic groups, however. Race and BMI appeared to have no impact on reporting frequency. This reviewer believes the risk-benefit still favors eluxadoline in the demographic groups assessed, and does not recommend any specific information related to drug-demographic interactions be included in the labeling at this time.

7.5.4 Drug-Disease Interactions

Hepatic Dysfunction:
Patients were excluded from the phase 2 and 3 studies if they had an ALT/AST >3 times the upper limit of normal or total bilirubin >3 mg/dL, with the exception of Gilbert's syndrome, at Prescreening. In addition, patients were excluded if they had an unstable hepatic condition. The Applicant provided a pooled summary of AEs based on elevated ALT (>1 to <3 x ULN) at baseline as well as elevated total bilirubin at baseline (>ULN but < 3mg/dL). In the pooled phase 2 and 3 studies, 500 patients had elevated ALT at baseline, 137 (17.2%) from the 75mg arm, 186 (18.9%) from the 100mg arm, and 177 (18.0%) from the placebo arm. Table 65 below shows overall adverse events in patients with hepatic impairment, as well as adverse events from the most common SOCs.

Table 65: Safety in Patients With Hepatic Impairment: Pooled Phase 2 and 3 Studies

n (%)	Eluxadoline 75 mg BID	Eluxadoline 100 mg BID	Placebo BID
Number of patients in safety analysis set	**807**	**1032**	**975**
Number of patients with at least 1 adverse events	486 (60.2)	575 (55.7)	533 (54.7)
Gastrointestinal disorders	242 (30.3)	273 (26.5)	185 (19.0)
Infections and infestations	199 (24.7)	222 (21.5)	230 (23.6)
Nervous system disorders	81 (10.0)	112 (10.9)	99 (10.2)
Number of patients with elevated ALT at baseline[a]	**137**	**186**	**177**
Number of patients with elevated baseline ALT and at least 1 adverse events	83(60.6)	114 (61.3)	92 (52.0)
Gastrointestinal disorders	37 (27.0)	60 (32.3)	39 (22.0)
Infections and infestations	35 (25.5)	48 (25.8)	41 (23.3)
Nervous system disorders	14 (10.2)	22 (11.8)	20 (11.3)
Number of patients with elevated bilirubin at baseline[b]	**21**	**32**	**28**
Number of patients with elevated baseline bilirubin and at least 1 adverse events	10 (47.6)	18 (56.3)	17 (60.7)
Gastrointestinal disorders	3 (14.3)	7 (21.9)	9 (32.1)
Infections and infestations	5 (23.8)	6 (18.8)	10 (35.7)
Nervous system disorders	2 (9.5)	6 (18.8)	4 (14.3)

Source: Applicant ISS Amendment Tables 2.29, 2.45 and 2.45a
[a] Patients with ALT > 3 x ULN were excluded from the studies, therefore elevated bilirubin at baseline includes those patients with total bilirubin > ULN but < 3 x ULN
[b] Patients with total bilirubin >3mg/dL were excluded from the studies, therefore elevated bilirubin at baseline includes those patients with total bilirubin > ULN but < 3 mg/dL

Hepatic Impairment:
The Applicant completed a Phase 1 study (CPS-1005) comparing eluxadoline exposures in subjects with varying degrees of hepatic impairment to that in healthy subjects after a single 100-mg dose of eluxadoline. Patients were classified as normal hepatic function (n= 15) or mild (n=6), moderate (n=6), and severely hepatically impaired (n=3), based on the Child-Pugh classification system (Class A, B, and C

respectively). In this study, eluxadoline total exposures were elevated on average 6-fold, 4-fold, and 16-fold in subjects with mild, moderate, and severe hepatic impairment, respectively. There were no deaths or AEs leading to study drug discontinuation.

Overall, 14 subjects (46.7%) reported AEs. Adverse events were reported by 5 subjects (83.3%) in the mild hepatic impairment cohort, 4 subjects (66.7%) in the moderate hepatic impairment cohort, 3 subjects (20.0%) with normal hepatic function, and 2 subjects (66.7%) in the severe hepatic impairment cohort. Dizziness was the most frequently reported AE and was reported by 2 subjects (33.3%) in the mild hepatic impairment cohort, 1 subject (16.7%) in the moderate hepatic impairment cohort, and 1 subject (33.3%) in the severe hepatic impairment cohort. There were 2 serious AEs reported. One subject with mild hepatic impairment experienced an acute MI which occurred (b) (6) days after study drug administration and was assessed as not related to study drug. One patient with severe hepatic impairment experienced an SAE of ileus 4 days after study drug administration which was assessed as related to study drug.

Renal Impairment:
Patients with unstable renal disease as well as hemoglobin <10 g/dL for women and <12 g/dL for men were excluded from the study. The safety profile in patients with mild to moderate renal dysfunction was similar to the overall safety population.

Reviewer Comments: The overall safety profile in patients with hepatic impairment at baseline, defined as either an elevated ALT or elevated total bilirubin at baseline was similar to the general safety population. The overall number of patients with AEs was comparable across treatment groups. The safety profile in patients with hepatic impairment defined by Child/Pugh classification was assessed in a Phase 1 study. This study showed significantly increased eluxadoline concentration in patients with hepatic impairment. AE profiles are difficult to compare, given the small number of patients, however the SAE of ileus in a patient with severe hepatic impairment appears likely related to treatment and was likely impacted by the high drug exposure. Given the supratherapeutic concentrations seen in patients with hepatic impairment and the lack of repeat dose safety information, contraindicating in patients with hepatic impairment, as defined by Child/Pugh classification seems appropriate.

7.5.5 Drug-Drug Interactions

Loperamide Use:
Overall, 829 patients in the Safety Analysis Set from Studies IBS-3001 and IBS-3002 used at least 1 dose of rescue medications (272, 262, and 295 patients in the 75mg, 100mg, and placebo groups, respectively). There was a slightly higher incidence of overall GI AEs in patients with rescue medication use compared with the full safety set, however, the incidence of GI AEs leading to study discontinuation and the incidence of GI SAEs was similar in patients with rescue medication use compared with the full

safety set. **Table 66** compares GI AEs in patients in the overall safety population and in patients with rescue medication use.

Table 66: GI Adverse Events in Full Safety Set and in Patients With Loperamide Rescue Medication Use

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

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

Importantly, loperamide use was used only as needed for acute management of diarrhea during eluxadoline clinical development. The summary provided in Table 63 does not account for the timing of rescue medication use. **Table 67** provides a summary of the incidence of select GI adverse events with onset dates 0-1 days, 2-3 days, 4-7 days, 8 – 14 days, and > 14 days after the most recent use of loperamide.

Table 67: Summary of Select Gastrointestinal Adverse Events with Onset Dates After Rescue Medication Loperamide Use

Preferred Term Time of Onset from loperamide use	Eluxadoline 75mg BID (N=272) n (%)	Eluxadoline 100mg BID (N=262) n (%)	Placebo BID (N=295) n (%)
Nausea	11 (4.0)	11 (4.2)	8 (2.7)
Onset day 0 – 1after loperamide use	3 (1.1)	3 (1.1)	1 (0.3)
Onset day 2 – 3 after loperamide use	1 (0.4)	1 (0.4)	2 (0.7)
Onset day 4 – 7 after loperamide use	0	1 (0.4)	1 (0.3)
Onset day 8 – 14 after loperamide use	2 (0.7)	1 (0.4)	0
Onset day > 14 after loperamide use	6 (2.2)	7 (2.7)	4 (1.4)
Constipation	10 (3.7)	16 (6.1)	4 (1.4)
Onset day 0 – 1after loperamide use	2 (0.7)	2 (0.8)	1 (0.3)
Onset day 2 – 3 after loperamide use	1 (0.4)	1 (0.4)	0
Onset day 4 – 7 after loperamide use	2 (0.7)	2 (0.8)	0
Onset day 8 – 14 after loperamide use	1 (0.4)	4 (1.5)	0
Onset day > 14 after loperamide use	4 (1.5)	9 (3.4)	3 (1.0)
Abdominal pain	9 (3.3)	10 (3.8)	10 (3.4)
Onset day 0 – 1after loperamide use	2 (0.7)	3 (1.1)	4 (1.4)
Onset day 2 – 3 after loperamide use	1 (0.4)	0	1 (0.3)
Onset day 4 – 7 after loperamide use	1 (0.4)	0	1 (0.3)
Onset day 8 – 14 after loperamide use	2 (0.7)	0	0
Onset day > 14 after loperamide use	3 (1.1)	7 (2.7)	5 (1.7)

Source: Applicant response to Information Request dated 30Jan2015, Table 3

Use with OATP1B1 inhibitors:

Eluxadoline is a substrate of the hepatic uptake transporter OATP1B1, and coadministration with an OATP1B1 inhibitor (cyclosporine) increased eluxadoline exposure by approximately 5-fold in drug-drug interaction studies. OATP1B1 inhibitor use was uncommon in the eluxadoline clinical development program. Gemfibrizol was the only OATP1B1 inhibitor used concomitantly, and it was reported in only 13 of 3235 subjects enrolled in the eluxadoline clinical development program, 6 of 1032 patients receiving 100mg BID and 3 of 975 patients receiving placebo. There were no serious adverse events reported in these 13 patients.

Reviewer Comments: There was a slightly increased incidence of GI AEs in patients with loperamide rescue medication use, however, importantly there was no increase in SAEs or AEs resulting in study discontinuation. Furthermore, no clear association can be seen between the timing of loperamide rescue medication use and the reporting of GI adverse events. Given that both loperamide and eluxadoline have the potential to cause constipation, there is the potential for increased GI AEs; however, this reviewer does not believe the safety data support contraindicating the use of loperamide with eluxadoline. The label currently recommends patients exercise caution when administering eluxadoline with loperamide and recommends that patients use

loperamide occasionally for acute management of severe diarrhea and discontinue if constipation occurs. This reviewer agrees with the proposed labeling by the Applicant. Given the small number of patients who received concomitant OATP1B1 inhibitors during eluxadoline clinical development, no definitive conclusions can be made, however, no specific signal was seen in this small group of patients. The label currently states that the (b) (4) *. This reviewer agrees with the proposed labeling.*

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies were not performed.

7.6.2 Human Reproduction and Pregnancy Data

Trials of eluxadoline in pregnant or lactating women were not conducted for this NDA. Pregnant and lactating women were excluded from enrollment in the clinical development program, and women of childbearing potential were required to use an effective method of contraception during study participation. Any women who became pregnant during a trial were immediately discontinued from clinical trial presentation and were followed through to the outcome of their pregnancy.

Thirteen (13) women became pregnant in the Phase 3 studies, 7 were randomized to eluxadoline and 5 to placebo. One patient was never randomized and never received study drug. Outcome data for the 7 pregnancies in women receiving eluxadoline are shown in **Table 68** below.

Table 68: Pregnancy Outcomes for Women Who Received Eluxadoline

Study and Patient ID	Dose	Age	Date of last treatment	Estimated Date of Conception	Days on study drug	Pregnancy outcome
IBS-3001 268/0018	75mg BID	39	04Mar2014	Positive pregnancy test 12Feb2014, but was not reported to site until 05Mar2014. Withdrawn from the study.	252	Due date was projected to be (b) (6) she experienced rib fractures caused by physical abuse from her boyfriend. A pelvic ultrasound on 28Feb2014 confirmed a spontaneous abortion.
IBS-3001 359/0006	75mg BID	46	15Apr2014	Positive pregnancy test result 16Apr2014 and patient withdrawn from study. Patient reported a tubal ligation in 2008.	314	On 20Apr2014 the patient reported an induced abortion. On 02May2014, follow up labs included a negative pregnancy test.
IBS-3001 137/0001	100mg BID	35	17Jun2013	Positive pregnancy test result on 22Jul2013 and patient withdrawn from study.	309	Uncomplicated delivery of a 7.0 pound healthy baby at 39.3 weeks of gestation on (b) (6).
IBS-3001 309/0032	100mg BID	34	10May2014	Positive pregnancy test on 12May2014 and patient withdrawn from study.	304	Due date was projected to be (b) (6). Patient had a spontaneous miscarriage on 30May2014. Patient had a history of 2 prior miscarriages.
IBS-3002 580/0006	75mg BID	28	26Mar2013	Before 17Apr2013. Patient completed the 26-week double-blind efficacy portion and was in the placebo washout when she became pregnant. Positive pregnancy test 18Apr2013. Patient was withdrawn from the study.	183	Uncomplicated delivery of a 5 pound, 9 ounce healthy baby at 39 weeks gestation. Patient had hypertension during her pregnancy and was treated with labetalol 200mg daily.
IBS-3002 625/0001	75mg BID	29	21Feb2013	Date of last menstrual period was (b) (6) and positive pregnancy test on 21Feb2013. Patient was withdrawn from the study.	129	Uncomplicated delivery of a 7 pound, 1 ounce healthy baby at 40.1 weeks gestation on (b) (6).
IBS-3002 850/0004	100mg BID	25	10Jan2013	22Jan2013 – positive pregnancy test 04Apr2013. Patient was withdrawn from the study.	39	Uncomplicated delivery of a 8 pound, 4 ounce healthy baby at 39.2 weeks gestation.

Source: Applicant Integrated Summary of Safety Table 12-7.

Reviewer comment: In developmental toxicity studies, there were no external, visceral, or skeletal abnormalities in rat or rabbit fetuses attributed to eluxadoline. In male and female fertility and early embryonic development study in rats, fertility was unaffected by treatment, and in an oral pre- and post-natal development study in rats, the NOEL for dams and offspring was 1000mg/kg/day, the highest dose level evaluated. Eluxadoline was secreted in the milk of lactating rats in a dose-dependent manner when given doses much higher than what would be administered to humans. The data from unplanned pregnancies during the eluxadoline clinical development does not show any teratogenicity. The 2 spontaneous Abs that occurred in women receiving eluxadoline were significantly confounded (1 suffered significant physical abuse of her chest/abdomen prior to spontaneous Ab, and the other had a history of 2 spontaneous Abs, so it is difficult to make any assessments based on this information. At this time, DPMH is not recommending any additional studies related to the potential impact of eluxadoline during pregnant and nursing women, however, a pregnancy registry and/or milk and serum lactation study could be considered in the future.

7.6.3 Pediatrics and Assessment of Effects on Growth

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 and a Deferral of Pediatric Study for pediatric patients ≥ 6 to < 17 and 11 months.

Reviewer comment: The applicants waiver and deferral request appear appropriate to this reviewer. The Applicant's Pediatric Study Plan was previously reviewed, presented to the Pediatric Research Committee (PeRC), and agreed upon with the Applicant. The final determination of waiver and deferral will be made upon presentation to the Pediatric Research Committee (PeRC) in March, and an addendum to my review will be provided, as necessary.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose: There were no cases of intentional or unintentional overdose with eluxadoline during the clinical development program. The maximum tolerated dose was 1500mg in men and 1000mg in women, 10 times the proposed marketed dose. The adverse event profile of eluxadoline appears similar across dose groups, with the exception of gastrointestinal AEs which may increase with increasing dose. This is consistent with the anticipated local GI action of the product.

Drug Abuse Potential:

Abuse potential studies were completed using oral and intranasal eluxadoline. Intravenous abuse potential studies were felt to be unethical due to safety concerns. The Applicant did complete a study self-injection study in Rhesus monkeys. Monkeys

discriminated injected eluxadoline as a Mu opioid and work for continued injections of it. The human abuse potential studies are summarized below.

Study CPS-1006 was a randomized, double-blind, double-dummy, placebo- and active-controlled, 6-period, crossover study that evaluated the oral abuse potential, safety, tolerability, and PK of eluxadoline versus placebo and oxycodone immediate release (IR) in healthy nondependent recreational opioid users. Subjects received single doses of eluxadoline (100, 300, and 1000mg), single doses of oxycodone IR (30 and 60mg), and placebo over 6 periods. Forty subjects were enrolled and 33 completed all treatment periods.

Overall, 100% of subjects had AEs with 60mg oxycodone IR, 94.6% with 30mg oxycodone IR, 77.8% with 300mg eluxadoline, 69.4% with 1000mg eluxadoline, and 48..6% with 100mg eluxadoline and with placebo. The most common AEs with eluxadoline were in the nervous system SOC (31.4% 100mg, 52.8% 300mg, and 30.6% 1000mg). **Table 69** below is a summary of select AEs in the nervous system and psychiatric disorders SOC from Study CPS-1006.

Table 69: Incidence of Select Adverse Events – Safety Analysis Set from Study CPS-1006

	Treatment at Onset of Adverse Event					
System Organ Class/ Preferred Term	Eluxadoline 100mg (N = 35)	Eluxadoline 300mg (N = 36)	Eluxadoline 1000mg (N = 36)	Oxycodone 30mg (N = 37)	Oxycodone 60mg (N = 37)	Placebo (N = 37)
Any Adverse Event	17 (48.6%)	28 (77.8%)	25 (69.4%)	35 (94.6%)	37 (100.0%)	18 (48.6%)
Nervous System Disorders	11 (31.4)	19 (52.8%)	11 (30.6%)	20 (54.1%)	24 (64.9%)	9 (24.3%)
Disturbance in attention	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)	0 (0.0%)	0 (0.0%)
Dizziness	0 (0.0%)	1 (2.8%)	0 (0.0%)	4 (10.8%)	7 (18.9%)	0 (0.0%)
Sedation	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (2.7%)	1 (2.7%)
Somnolence	11 (31.4%)	15 (41.7%)	7 (19.4%)	14 (37.8%)	15 (40.5%)	7 (18.9%)
Psychiatric Disorders	5 (14.3%)	8 (22.2%)	10 (27.8%)	28 (75.7%)	27 (73.0%)	3 (8.1%)
Euphoric mood	5 (14.3%)	7 (19.4%)	10 (27.8%)	28 (75.7%)	27 (73.0%)	2 (5.4%)

Source: Applicant Clinical Study Report CPS-1006, Table 14.3.1.2
Percentage is calculated based on the number of subjects per treatment group as the denominator. Subjects are counted only once per System Organ Class or Preferred Term.

Study CPS-1010 was a randomized, blinded, placebo- and active-controlled, 6-period, crossover study that evaluated the intranasal abuse potential, safety, tolerability, and

PK of crushed eluxadoline versus crushed oxycodone IR and matching placebo in healthy nondependent recreational opioid users with a history of intranasal abuse. Subjects self-administered via insufflation eluxadoline (100 and 200 mg), oxycodone IR (15 and 30mg), lactose placebo weight matched to oxycodone IR, and placebo weight matched to 200 mg eluxadoline. Thirty-six subjects were enrolled and 31 completed all treatment periods.

The most common AEs for both eluxadoline doses (100mg and 200mg) were nasal congestion (37.5% and 50.0%), dysgeusia (31.3% and 31.3%), and euphoric mood (21.9% and 18.8%). For both oxycodone doses (15mg and 30mg), the most common AEs were euphoric mood (43.8% and 65.6%), somnolence (28.1% and 50.0%), and pruritis (31.3% and 34.4%). Intranasal eluxadoline was associated with significant disliking versus placebo and oxycodone IR on subjective measures. Subjects showed no willingness to take eluxadoline again, and ratings of intranasal discomfort and nasal AEs suggest that negative nasal side effects would mitigate the risk of abuse with this route of administration.

Withdrawal and Rebound: There was no evidence of withdrawal or rebound potential with eluxadoline during the clinical development program. Please see Section 7.3.5 Submission Specific Primary Safety Concerns for a discussion of withdrawal and rebound potential with eluxadoline.

Please see also the CSS primary review by Alan Trachtenberg, MD.

Reviewer Comments: The Applicant suggests that Study CPS-1006 demonstrates that single oral doses of eluxadoline up to 1000mg have significantly less abuse potential than oxycodone IR in recreational opioid users. This reviewer agrees; 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 only 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 impact on patients using eluxadoline as indicated. It is difficult to say definitively, however, whether there is any potential for abuse, though clearly the risk appears to be significantly less than with pure mu agonists. 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?

A recommendation on potential scheduling of eluxadoline will be made by the Controlled Substance Staff, and a final decision will be made following approval of the product.

7.7 Additional Submissions / Safety Issues

There were no additional submissions/safety issues.

8 Postmarket Experience

There is no postmarket experience with this drug because it is not approved at the time of this review.

9 Appendices

Appendix 1: Benefit-Risk Assessment Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons (Implications for regulatory decision making)
Analysis of Condition	• Irritable bowel syndrome affects up to 20% of adolescents and adults in North America, and diarrhea predominant IBS (IBS-d) accounts for ~ 1/3 of all cases (Ward A 2012) • IBS is not a life-threatening condition; however, its 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. (Thompson 1999)	IBS-d does not cause mortality, however, it can have a significant impact on quality of life and is associated with significant direct and indirect expenses
Current Treatment Options	• The only FDA-approved therapy for this indication is alosetron which is approved only for women with severe IBS-d. Alosetron is marketed under a restricted distribution REMS due to safety concerns related to serious complications of constipation and ischemic colitis • Loperamide is a frequently used antidiarrheal used in the management of IBS-d, but it has not been shown to reduce abdominal pain associated with IBS-d and is associated with treatment related constipation	There is a need for additional treatment options for IBS-d, particularly for men with the condition given the lack of approved therapies for this subgroup.
Clinical Benefit	• IBS-3001 was a 52-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing eluxadoline 75mg and 100mg BID with placebo in 1282 patients with IBS-D. IBS-3001 included efficacy assessments at 12 and 26 weeks and continuation to Week 52 for long term double blind safety data. o The primary endpoint was the proportion of composite responders over the initial 12 week double-blind period. A patient was a composite responder if he or she met the daily response criteria for at least 50% of the days with diary entries during Weeks 1 – 12. A patient was a daily	Eluxadoline 75mg and 100mg BID are effective in the treatment of adult patients with IBS-D, as was demonstrated in 2 well-controlled phase 3 studies. The 100mg dose showed slightly higher efficacy vs placebo, compared to the 75mg dose vs placebo. For example, while a higher proportion of patients in the 75mg group were composite responders for each 4-week interval

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons (Implications for regulatory decision making)
	responder if he or she met both of the following criteria: ▪ Daily pain response: worst abdominal pain scores in the past 24 hours improved by ≥ 30% compared to baseline, where baseline was the average of daily worst abdominal pain score the week prior to randomization ▪ Daily stool consistency response: BSS score < 5 or the absence of a bowel movement if accompanied by ≥ 30% improvement in worst abdominal pain compared to baseline pain. ○ Secondary endpoints included separate analyses of composite responders over each 4 week interval during double-blind treatment, pain responders and stool consistency responders, as well as some global symptom and QoL assessments ○ 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 (23.9% vs 17.1%, p = 0.014). Results from a variety of sensitivity analyses were consistent. ○ The proportion of composite responders was significantly higher over each 4-week interval for the 100mg and compared to placebo and for most of the 4-week intervals for the 75mg group compared to placebo. The proportion of stool consistency responders for the 75mg and 100 mg treatment groups was significantly higher than placebo over the interval from Weeks 1 – 12 for both treatment groups, as well as over the interval from Weeks 1 – 26 for the 100mg treatment group. The proportion of pain responders for the 75mg and 100 mg	in study IBS-3001, this difference did not always reach statistical significance. Importantly, both doses met their primary endpoint and are effective.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons (Implications for regulatory decision making)
	treatment groups was higher than placebo over the interval from Weeks 1 – 12, however, the differences did not reach statistical significance. • IBS-3002 was a 26-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study with 4-week, single-blind withdrawal period comparing eluxadoline 75mg and 100mg BID with placebo in 1146 patients with IBS-D. o The primary endpoint was identical to IBS-3001 (proportion of composite responders over the initial 12 weeks double-blind treatment). o The secondary endpoints were identical to IBS-3002. o A significantly higher proportion of patients in both eluxadoline arms were composite responders compared to placebo when looking through Week 12 (28.9% 75mg, 29.6% 100mg, vs 16.2% placebo) and through Week 26 (30.4% 75mg, 32.7% 100mg, vs 20.2%). Results from a number of sensitivity analyses were consistent. o The proportion of composite responders was significantly higher over each 4-week interval for both the 100mg and 75mg group, compared to placebo. The proportion of stool consistency responders for the 75mg and 100mg treatment groups was significantly higher than placebo over both treatment intervals. The proportion of pain responders for the 75mg and 100 mg treatment groups was higher than placebo over the interval from Weeks 1 – 12, however, the differences did not reach statistical significance.	
Risk	• A total of 2562 subjects have received at least 1 dose of oral eluxadoline during the clinical development program. A total of 1032 patients received at least 1 dose of 100 mg eluxadoline, 505 patients completed 6 months of treatment with 100mg eluxadoline, and 243 patients completed 12 months of treatment with eluxadoline.	The overall safety profile of eluxadoline is acceptable for IBS-D treatment and may have less risk for serious complications of constipation and ischemic colitis than alosetron, the only currently approved therapy for IBS-D. GI AEs were more

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons (Implications for regulatory decision making)
	• Overall incidence rates for AEs were comparable across treatment groups during Phase 2 and 3 studies (49.3% 75mg, 44.3% 100mg, 42.4% placebo). The most common AEs reported were within the GI disorders and infections and infestations SOCs. Constipation occurred in a higher percentage of patients in eluxadoline treatment arms (7.4% 75mg and 8.1% 100mg) than placebo (2.5%). There was also a slightly higher incidence of abdominal pain in the eluxadoline treatment arms compared to placebo, early in the course of treatment. • The overall rates of serious AEs were low and the proportion of patients with SAEs were similar across treatment arms (4.2% 75mg, 4.0% 100mg, 2.6% placebo). Pancreatitis was the most commonly reported SAE in eluxadoline treated patients. • There were 9 adjudicated cases of pancreatitis in patients who received eluxadoline, 3 of which were adjudicated as consistent with sphincter of Oddi (SO) spasm and 4 cases associated with EtOH. In addition, there were 9 adjudicated hepatobiliary events in patients who received eluxadoline, all of which were consistent with SO spasm. Eight (8) of these cases occurred in patients with absent gallbladder. • There was no imbalance of AEs suggestive of abuse potential and no indication of symptoms related to withdrawal on discontinuation of eluxadoline.	frequent with eluxadoline than placebo, but these were generally mild in intensity. Similar to other opioids, there is an increased risk of adverse events associated with Sphincter of Oddi dysfunction with eluxadoline. These events (pancreatitis and hepatobiliary events) were reversible on discontinuation of therapy. Patients with a history of pancreatitis, alcoholism, or SOD disease are contraindicated from the use of eluxadoline. Patients with prior cholecystectomy are at higher risk for AEs associated with SOD, and this is included in the W&P section of the label. There was no evidence of adverse events associated with abuse or withdrawal during eluxadoline clinical development.

Risk Management	• The Applicant provided a non-REMS risk minimization strategy which included the following goals:
	  ○ To inform prescribers of the risks of pancreatitis and hepatobiliary events related to sphincter of Oddi spasm events and to educate them on appropriate patient selection in order to minimize the occurrence of these events.
	  ○ To closely monitor the safety profile after launch of eluxadoline with a focus on these events of special interest.
	• The Applicant's risk minimization strategy to inform patients
		At this time, no formal postmarketing Risk Evaluation and Mitigation Strategy (REMS) is required for eluxadoline. The Applicant's proposed non-REMS risk minimization strategy is acceptable.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons (Implications for regulatory decision making)
	and educate prescribers includes the Full Prescribing Information, as well as a Medication Guide and a risk communication guide.	

Benefit-Risk Summary and Assessment

It is the assessment of this reviewer that the benefits of eluxadoline outweigh the risks in the treatment of adult patients with irritable bowel syndrome with diarrhea (IBS-D). The Applicant adequately characterized the safety profile of eluxadoline, and the Full Prescribing Information, as well as a 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 are sufficient to monitor the safety profile of eluxadoline following its approval and marketing. A decision on the scheduling of eluxadoline will be made following its approval.

Appendix 2: Literature Review/References

See footnotes.

Appendix 3: Labeling Recommendations

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.

Appendix 4: Advisory Committee Meeting

There was no FDA Advisory Committee Meeting held for discussion of NDA 206940.

Appendix 5: Detailed Events of Pre-Submission Regulatory History

- November 21, 2007: IND 79,214 submission for eluxadoline

- March 16, 2010: Type C End of Phase 1 Meeting. The purpose of this meeting was to discuss the nonclinical and clinical development plans and endpoints for the proposed phase 2 study. Agreed were:
    - Co-primary endpoints of abdominal pain and improvement in stool consistency are acceptable.
    - Daily pain item would query patients about their "worst abdominal pain in the last 24-hours".
    - Both pictorial and verbal descriptors of stool consistency for the BSS should be included when evaluating stool consistency. The Agency advised the Sponsor to submit the patient-reported daily symptom measure for review.
    - IBS-Quality of Life (IBS-QOL), IBS-Adequate Relief Item, IBS Symptom Severity Scale (IBS-SSS), and EQ-5D could be used as exploratory endpoints (b) (4)
    - Phase 3 trials will need to be 8 – 12 weeks in duration with safety data of at least 1 year duration

- July 8, 2010: Advice letter to sponsor (IND 79,214) regarding abuse potential study requirements.
    - A dedicated human abuse potential study using intravenous administration of JNJ-27018966 is required. The Profile of Mood States (POMS) provides a general overview of mood states and their fluctuation and will not provide an accurate assessment of the abuse potential.

  - Evaluate the extractability and feasibility of preparing JNJ-27018966 for abuse purposes by alternative routes of administration including snorting, injection, and chewing.

- January 19, 2011: Fast track designation granted for JNJ-27018966 in the treatment of diarrhea-predominant irritable bowel syndrome

- July 5, 2011: Type C meeting to introduce interim analysis results from the phase 2 study and discuss proposed endpoints for phase 3 studies.
  - The Agency did not agree with the proposed BSS responder definition (b) (4) and recommended a BSS responder definition of "a reduction of ≥50% in the number of days per week with BSS scores ≥6 as compared to baseline."
  - The Agency recommended an abdominal pain responder definition of "a decrease in the weekly average of the worst abdominal pain in the last 24 hours score of ≥30%, and at least a 2 point improvement on the pain scale."
  - An overall responder should be defined as a responder for the composite endpoint for at least 50% of the weeks of the trial. The Sponsor should also demonstrate that the treatment effect is durable throughout the treatment phase of the trial (i.e., 2 of 4 weeks of each month)
  - For the primary efficacy comparison, subjects lost to follow-up or subjects with insufficient data should be treated as non-responders.
  - As per ICHE1A guidelines, the safety database at the time of NDA submission should include greater than 1000 subjects overall exposed to the marketed dose, with 300 to 600 patients exposed for at least 6 months and at least 100 exposed for 1 year.
  - It is acceptable to define patients with BSS ≥ 5.5 as IBS-D.

- September 27, 2011: Type B End of Phase 2 Meeting to discuss overall Phase 3 study design, including primary endpoints, responder definitions and associated analyses.
  - Completed, ongoing, and planned nonclinical studies appear sufficient to support an NDA
  - The primary efficacy endpoint should build upon the definition of a weekly responder and an overall/study responder would be defined as a subject who is a weekly responder for at least 50% of study weeks. To be a composite responder, a patient must be a responder in BOTH the abdominal pain and BSS co-primary endpoints.
  - For the primary analysis, subjects with fewer than 4 diary days per week be considered missing for the whole week and classified as treatment failures for that week (the Sponsor's proposed threshold of 5 days per week is also acceptable).

  - The primary analysis should be based on the ITT population defined by all randomized subjects. All subjects randomized and with at least one post-randomization evaluation would constitute a modified ITT population.
  - The proposed eligibility criteria are acceptable (patients meeting Rome III criteria for IBS-d who have clinical manifestations of sufficient intensity at baseline to allow demonstration of a meaningful clinical improvement).
  - Include in the protocol specific instructions for the use of rescue medications. The protocol should also specifically define the adverse event of constipation based on the BSS and the number of days involved.

- January 24, 2012: Type C EOP2 CMC meeting, written response only
  - The purpose of the meeting was to discuss the Sponsor's CMC development program and seek FDA concurrence on the acceptability

- May 22, 2012: Advice letter to sponsor
  - A waiver for IRB requirements for the use of JNJ-27018966 in a foreign investigational study
  - Statistics provided recommendations on the phase 3 protocols to stratify by center and/or region and that the ITT population should include all randomized subjects

- June 11, 2012: Advice letter to sponsor regarding renal impairment studies.
  - FDA agreed that a renal impairment study could be performed after NDA submission and approval.
  - It is acceptable to first conduct a study in patients with ESRD and then determine if a study in patients with a lower degree of renal impairment is necessary; however, the initial study should be done in patients with ESRD not yet on dialysis

- June 13, 2012: Advice letter to sponsor regarding phase 3 protocols.
  - The Agency agreed that the submitted protocols 3001 and 3002 are appropriate for pivotal trials and adhere to EOP2 agreements and confirmed that the finalization of the IBS guidance will not impact the FDA's acceptance of the proposed protocols.

- December 6, 2012: Type C meeting, written response only to discuss all aspects for assessing the abuse liability of eluxadoline.
  - The Agency does not recommend performing an IV human abuse potential study due to serious safety concerns in the IV monkey studies where 2 monkeys suffered serious adverse events that resulted in the death of one of the monkeys. Due to the safety concerns, CSS will rely on the results of the animal self-administration study for assessing the abuse potential of JNJ-27018966.

- The Agency does not agree with performing a [redacted] (b) (4)
- The Sponsor should assess the BA of the product when "snorted". This should be done using in vitro or preclinical studies.
- The Agency agrees with the use of the Subjective Opiate Withdrawal Scale (SOWS) to assess withdrawal during Phase 3 trials.
- The Agency's primary concern is the abuse potential of JNJ-27018966 when administered via an alternative route(s) of administration. The Sponsor should examine in detail the vulnerability of the to-be-marketed formulation to physical manipulation and chemical extraction of the active ingredient. The in vitro abuse potential assessment should include:
  - Assessment of ways that tampering can produce a preparation suitable for intranasal or IV abuse
  - Assess the ease of extraction from intact and crushed formulation using solvents of different polarity and pH. Chemical extraction should be done under rigorous agitation and assessed at multiple time points.
  - Evaluate the effect of elevated solvent temperature on extraction.

- October 10, 2012: Advice letter to sponsor related to clinical pharmacology.

- November 2, 2012: Advice letter on thorough QTc study
  - The Agency did not agree with the dose selection for the proposed thorough QTc study and recommends a single dose study [redacted] (b) (4) The ECG/PK collections times were adequate. As Cmax in the fasted state has been sown to be ~3-fold that in the fed state, we recommended that JNJ-27018966 be administered in the fasted state.

- October 15, 2013: Type C face-to-face meeting to discuss the overall proposed pediatric study plan for eluxadoline, to include the design of the studies planned and associated timelines.
  - The Sponsor will need to conduct dose-ranging studies in children to establish dosing, followed by at least one safety and efficacy trial at the identified dose(s). [redacted] (b) (4)
  - [redacted] (b) (4)

- The proposed eligibility criteria are acceptable, however, the Agency does not agree with [redacted] (b) (4)
- The Agency agreed that studies could be deferred until NDA approval

- December 13, 2013: Advice letter
  - The Agency provided responses to Sponsor questions regarding Loss to Follow-Up, specifically that
    - The absence of a death certificate is reasonable evidence the patient remains alive and is LTFU
    - The rates of patients LTFU provided (2 – 3.4%) is within the range seen in other IBS trials

- January 31, 2014: Type C, written response only meeting to discuss the ISS/ISE
  - The plan to pool all studies in the ISS, except 27018966CPS101 which did not have an oral ROA is acceptable. For patients randomized more than once, it is acceptable to analyze their safety data according to the treatment received during the time a given event occurred.
  - The agency agrees with subgroups based on demographics, baseline characteristics, medical history, and concomitant medications, specifically examine the AE profile of subjects who took CNS drugs concomitantly
  - We agree with pooling data from the 2 phase 3 studies in the ISE, however, the results from the ISE will be exploratory only

- February 25, 2014: Type B Pre-NDA CMC Meeting
  - The purpose of this meeting was to discuss the Quality section of the eluxadoline tablet NDA submission

- March 24, 2014: Advice letter, clarification from pre-NDA CMC meeting
  - It will be acceptable to submit the NDA with 6 months of stability data for drug substance packaged in [redacted] (b) (4) packaging and 9 months of data for drug substance packaged in [redacted] (b) (4) packaging, provided that within 30 days of initial submission three additional months of stability data in each of these packages is provided.

- April 22, 2014: Type B Pre-NDA Meeting
  - The Sponsor will conduct a renal impairment study post-approval.
  - The extent and duration of exposure to eluxadoline presented by the sponsor appeared adequate to meet ICH requirements (2562 subjects had been exposed to eluxadoline, including 1110 for at least 6 months and 170 for at least one year at doses of 75 to 100mg bid).
  - The Agency agreed with the Sponsor's plan to provide safety narratives for all deaths, serious adverse events, and certain other significant adverse events (AEs) as a part of the clinical study reports from our Phase

3 studies in the NDA and requested CRFs and narratives for all dizziness AEs, in addition to the significant AEs proposed.

- The Sponsor will define sphincter of Oddi spasm to provide a rationale for the apparent association between acute hepatobiliary and pancreatitis events seen with their drug in the NDA.
- The Agency agreed with the use of complete patient profile, rather than a CRFs, for patients enrolled in phase 2 and 3 studies for certain AEs, as the patient profile coalesces all patient information from 3 electronic sources (eCRF, labs, and patient diaries).
- FDA stated that all IBS-3001 safety data should be included in the initial NDA submission. The Agency and Sponsor agreed that if the NDA submission is filed in June without complete safety data, a major amendment with the final ISS could be submitted as the 120-day safety update. This would be considered a major amendment and would result in a 3 month clock extension.

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

/s/

LAURIE B MULDOWNEY
02/25/2015

RUYI HE
02/25/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 206940 **Applicant: Furiex** **Stamp Date: June 27, 2014**

Drug Name: eluxadoline **NDA/BLA Type: original submission**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCDT Format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Included in Clinical Overview in 2.5.6
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505 (b)(1) – original NME
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number*: IBS-2001* Study Title: *A randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multicenter study to evaluate the efficacy, safety, and tolerability of JNJ-27018966 in the treatment of patients with irritable bowel syndrome with diarrhea*	X			The Agency agreed to the design of the dose ranging study.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Sample Size: 789 Arms: 4 Location in submission: 5.3.5.1				
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 IBS-3001 Indication: IBS-D Pivotal Study #2 IBS-3002 Indication: IBS-D	X			2 adequate and well-controlled studies in adult patients with IBS-D
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Conforms to FDA comments in meeting minutes as well as FDA Guidance for IBS.
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	The phase 2 study was conducted in the US only, & phase 3 studies were conducted in the US, Canada, and the UK
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			AE dataset includes PT for each event but does not include HLT, HLGT, or LLT
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			CPS-1008 (5.3.4.1)
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MEDDRA version 11.1 used for coding AEs
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			Sphincter of Oddi spasm, pancreatitis, fall/syncope/traffic accidents, withdrawal symptoms
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Renal impairment study will be completed post-approval, no other special studies requested
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			Section 1.11.4 Abuse Potential Evaluation Report
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	The phase 2 study was conducted in the US only, & phase 3 studies were conducted in the US, Canada, and the UK
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			No SDTM Reviewer's guide. CDISC used.
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			Patient profiles provided instead of CRF for certain AEs (includes info from 3 eCRF, labs, and patient diaries). Agency agreed
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			See above.
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			A form 3454 was completed with a listing of all Phase 3 trial investigators.
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			2.5.1.2 Summary of the Clinical Development Program and Timing of Application

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

n/a

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

• *We note that complete safety data is included for all patients from Study IBS-3001 only up to Week 26 and that complete safety data (through 52 weeks of dosing and 2 weeks of post-treatment follow-up) was not provided for this study with your NDA submission. As previously agreed upon during the preNDA meeting on April 22, 2014 and follow-up communication to the pre NDA meeting dated May 7, 2014, the FDA considers the application fileable, however, the remaining IBS-3001 safety data should be provided as an amendment to the NDA and should comprise updated ISS tables and a complete update of the ISS text. As a reminder, this submission will trigger a "major amendment" adding three months to the review clock.*

• *Please update the AE datasets for studies 3001 and 3002 to include all levels of the MEDDRA hierarchy. Similarly, please include all levels of the MEDDRA hierarchy in the updated ISS datasets which will be submitted with the 120-day safety update.*

Laurie Muldowney, MD	8/12/14
Reviewing Medical Officer	Date
Ruyi He, MD	8/12/14
Clinical Team Leader	Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

APPEARS THIS WAY ON ORIGINAL

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

/s/

LAURIE B MULDOWNEY
08/16/2014

RUYI HE
08/18/2014