Eluxadoline in the Treatment of Irritable Bowel Syndrome with Diarrhea

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ABSTRACT: Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by chronic abdominal pain and constipation (IBS-C), diarrhea (IBS-D), or a mixed pattern of altered bowel habits (IBS-M). It has a prevalence of 12% in North America with approximately one-third of patients having IBS-D in the United States. This subtype is associated with the poorest quality of life. A variety of treatment options exist, making a one-size-fits-all treatment strategy impossible. These treatment options alleviate one or more of the common IBS symptoms including abdominal pain and cramps, diarrhea, constipation, and bloating. These drugs include loperamide, antispasmodics, tricyclic antidepressants, alosetron, probiotics, and rifaximin. Eluxadoline is a μ-opioid receptor agonist and a δ-opioid receptor antagonist approved to treat adult patients with IBS-D. The aim of this study was to review eluxadoline for the treatment of IBS-D, including its pharmacology, clinical efficacy, safety, and current therapy.

KEYWORDS: irritable bowel syndrome, eluxadoline, diarrhea

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Background

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by chronic abdominal pain and constipation (IBS-C), diarrhea (IBS-D), or a mixed pattern of altered bowel habits (IBS-M). Other frequently reported symptoms include bloating, flatulence, and cramps. IBS is the most common reason that patients seek treatment from a gastroenterologist.[1] It has a prevalence of 12% in North America with approximately one-third of patients having IBS-D in the United States.[2,3] This subtype is associated with the poorest quality of life (QoL).[4]

The causes of IBS are multifactorial representing a variety of disease processes.[5] Etiology may include any of the following: genetic predisposition, visceral hypersensitivity, altered microbiota in the gastrointestinal (GI) tract, psychological stress, mucosal inflammation, and GI immune system activation possibly from an altered brain–gut axis.[6] IBS is diagnosed (1) using the Rome III criteria (Table 1) that assess symptom frequency, severity, and duration and (2) by ruling out celiac disease with celiac antibody testing unless the patient is greater than 50 years of age or has alarm symptoms in which case a colonoscopy or further investigation is warranted. Alarm symptoms include weight loss, rectal bleeding, anemia, and nighttime awakening due to symptoms.

A variety of treatment options exist that target the many underlying mechanisms of IBS, making a one-size-fits-all treatment strategy impossible. These drugs alleviate one or more of the common IBS symptoms including abdominal pain and cramps, diarrhea, constipation, and bloating. For IBS-D, these drugs include loperamide, antispasmodics, tricyclic antidepressants, alosetron, probiotics, and rifaximin. Some of the older drugs have been used for many years based on the results of poorly designed studies with limited evidence of efficacy and high placebo response rates.[7] In 2012, the US Food and Drug Administration (FDA) issued a guidance document that recommended using the FDA IBS responder end point as the primary end point for future IBS-C and IBS-D drug studies.[8] The FDA IBS responder end point measures a patient-reported outcome capturing several signs and symptoms instead of single-item measures historically used in IBS trials (satisfactory relief or the Subject Global Assessment of Relief). Since 2012, drug manufacturers seeking approval for new IBS drugs in the United States have used the FDA IBS responder end point. The American College of

Table 1. Rome III Criteria.

Recurrent abdominal pain or discomfort 3 days per month in the last 3 months associated with 2 or more of:
– improvement with defecation
– Onset associated with a change in frequency of stool
– Onset associated with a change in form of stool

Gastroenterology and the American Gastroenterological Association published treatment guidelines that provide either a weak/conditional or a strong recommendation and rate the quality of evidence (very low, low, moderate, or high) used to make the recommendation for the drugs used to treat IBS.[9,10]

Eluxadoline, approved to treat adult patients with IBS-D in 2015, is a μ-opioid receptor agonist and a δ-opioid receptor antagonist (Fig. 1). It is also a κ-opioid receptor agonist, but the implications of this activity are unclear. The dose of eluxadoline is 100 mg twice daily with food, but it should be reduced to 75 mg twice daily in patients who are unable to tolerate the 100 mg dose, without a gallbladder, receiving concomitant OATP1B1 inhibitors, or who have mild or moderate hepatic impairment.[11] It has only minimal systemic absorption, but the US Drug Enforcement Agency placed it in Class IV of the Controlled Substance Act, which means that it has a low abuse potential comparable to other drugs that are Class IV controlled substances.[12] In a double-blind placebo-controlled study of recreational opioid users, eluxadoline (oral and intranasal) compared to an oxycodone treatment arm and a placebo arm was found to have less abuse potential than oxycodone. The primary end point was the Drug Liking Visual Analog Scale (VAS). Oral eluxadoline resulted in a statistically significant higher Drug Liking VAS compared to placebo but not to oxycodone. In addition, nasal eluxadoline resulted in a similar Drug Liking VAS compared to placebo but a significantly lower Drug Liking VAS than oxycodone.[13]

The purpose of this article is to review the use of eluxadoline for the treatment of IBS-D, including its pharmacology, clinical efficacy, safety, and its place in current therapy.

Eluxadoline Drug Class and Mechanism of Action

There are three major opioid receptors in the GI tract, μ, δ, and κ. Activation of the opioid receptors in the enteric nervous system of the GI tract leads to inhibition of smooth muscle (μ-opioid receptor), inhibition of circular muscle (δ-opioid receptor), and decreased GI propulsion and visceral sensitivity (κ-opioid receptor). Eluxadoline is a synthetic opioid receptor modulator, a high-affinity μ-opioid receptor agonist, and a δ-opioid receptor antagonist in the GI tract only. It is likely a κ-opioid receptor agonist, but the implications of this activity are unclear. The activity at the δ- and κ-opioid receptors is believed to contribute to eluxadoline's reduced incidence of constipation. In contrast to eluxadoline, loperamide is an antidiarrheal agent with agonist activity at the μ-opioid receptor but no activity at the δ- or κ-opioid receptors. Constipation is a common adverse effect of loperamide.[14]

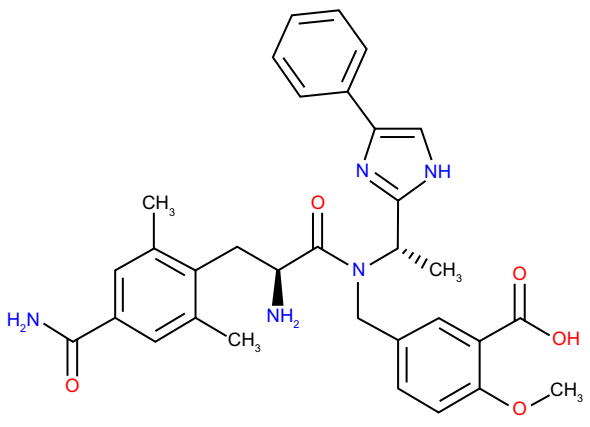

Figure 1. Eluxadoline chemical structure.

Eluxadoline Pharmacokinetics

The absolute bioavailability of eluxadoline is unknown, but it is believed that absorption into systemic circulation is minimal. Any drug that is systemically available is highly protein bound and is unlikely to be distributed widely due to the drug's local gut activity and minimal systemic absorption.[11] *In vitro* and *in vivo* assessments reveal no hepatic drug metabolism with the exception of an acyl glucuronide metabolite detected in urine following administration of a 1-g dose. In a single-dose study of radiolabeled eluxadoline 300 mg in healthy male volunteers, less than 1% of the total radioactivity was recovered in the urine within 192 hours and 82.2% was recovered in feces within 336 hours.[11,15] The mean eluxadoline plasma concentration increased by sixfold, fourfold, and 16-fold in patients with mild, moderate, and severe hepatic impairment following a single dose of 100 mg. As a result, a reduced dose of 75 mg twice daily is recommended for patients with mild to moderate impairment, defined as Child–Pugh class A or B. In patients with severe hepatic impairment (Child–Pugh class C), eluxadoline is contraindicated due to lack of safety information in these patients.[11]

Clinical Efficacy of Eluxadoline in the Treatment of IBS-D

A Phase 2, multicenter, randomized, double-blind, placebo-controlled study was conducted at 263 US treatment centers. In this dose-ranging study, a total of 807 patients were randomly assigned to treatment with eluxadoline (5, 25, 100, or 200 mg) or placebo (Table 2).[16] Following an initial screening period, eligible patients entered a two- to three-week pretreatment (baseline) period followed by a 12-week treatment period and a two-week posttreatment period. All patients were in the age group of 18–65 years and met the Rome III criteria for IBS-D; patients who reported using prohibited medications (eg, antibiotics, anticholinergics, cholestyramine, opioids, 5-HT3 antagonists, and 5-HT4 agonists) were required to have discontinued use at least 21 days prior to the treatment period. Patients who proceeded to the treatment period were allowed to continue stable doses of medications for depression, migraine headaches, anxiety, or other chronic conditions. During the treatment period, single-blind placebo rescue (weeks 1–4) and loperamide 2 mg/dose (weeks 5–12) was allowed for uncontrolled diarrhea and acetaminophen was allowed for uncontrolled abdominal pain (weeks 1–12). Loperamide doses were limited to four doses per 24 hours,

Table 2. Summary Data from Efficacy Trials of Eluxadoline for IBS-D.

REFERENCE	DESIGN	DURATION	SELECTED INCLUSION CRITERIA	TREATMENT	PRIMARY OUTCOME
Dove et al, Gastro 2013	Multicenter (263 sites), double-blind, placebo-controlled, randomized dose-ranging study	2–3 week pretreatment (baseline), 12 week treatment, and 2 week post-treatment periods	Male or female, ages 18–65 yr, IBS-D per Rome III criteria, mean daily WAP score ≥3.0, Bristol Stool Scale ≥5.5	Eluxadoline 5 mg (n = 105), 25 mg (n = 167), 100 mg (n = 163), and 200 mg (n = 160) vs. placebo (n = 159)	Decrease in the mean daily WAP scores by 30% from baseline and at least 2 points PLUS daily Bristol Stool Scale score of 3 or 4 on >66% of daily diary entries (% of patients): Eluxadoline 5 mg, 12.4 Eluxadoline 25 mg, 12.0# Eluxadoline 100 mg, 11.0 Eluxadoline 200 mg, 13.8# Placebo, 5.7
Lembo et al, NEJM 2016	Multicenter (IBS-3001, 295 sites; IBS-3002, 261 sites), double-blind, placebo-controlled, randomized, parallel-group trials	4 week pretreatment (baseline), 26 week treatment, and 2–4 week post-treatment periods	Male or female, ages 18–80 yr, IBS-D per Rome III criteria, mean daily WAP score >3.0, mean Bristol Stool Scale ≥5.5, and mean IBS-D global symptom score ≥2.0	Eluxadoline 75 mg (n = 810) and 100 mg (n = 809) vs. placebo (n = 809)	Decrease in ≥50% of days a reduction of >30% from mean baseline WAP score and Bristol Stool Scale score <5 (% of patients): 12 weeks (FDA endpoint)* Eluxadoline 75 mg, 26.2^ Eluxadoline 100 mg, 27.0^ Placebo, 16.7 26 weeks (EMA endpoint)* Eluxadoline 75 mg, 26.7^ Eluxadoline 100 mg, 31.0^ Placebo, 19.5

Notes: #$P < 0.05$ vs. placebo. ^$P < 0.001$ vs. placebo. *Represents pooled data from IBS-3001 and IBS-3002 studies.

seven doses per 48 hours, and 11 doses per any seven-day period.

The primary end point was the proportion of patients who achieved clinical response at week 4, defined as a decrease in the mean daily worst abdominal pain (WAP) scores from baseline by more than 30% and a change of at least 2 points, plus a daily Bristol Stool Scale score of 3 or 4 on more than 66% of daily diary entries for that week. Secondary end points included the proportion of patients achieving clinical response at week 12 and those achieving response to the individual WAP and stool consistency scores at weeks 4 and 12. Following the initiation of the study, the FDA issued guidance for outcome measures specific to IBS clinical trials. Post hoc analyses were conducted that incorporated these outcome measures to define daily responders. Specifically, participants were considered responders if for at least half of all days during the 12-week study their WAP score was reduced from baseline by at least 30% and they had either a Bristol Stool Scale score of <5 or had no bowel movement. Participant response was also evaluated using IBS global symptom score, IBS adequate relief, and QoL assessments.

Patients in the eluxadoline 25- (12.0%; $P = 0.041$) and 200-mg (13.8%; $P = 0.015$) groups had significantly improved composite (WAP and stool consistency) scores compared to placebo (5.7%) at week 4 and met the primary end point for the study. Similar improvements in the composite scores were seen in both the 5- (12.4%) and 100-mg (11.0%) groups, but these did not meet statistical significance ($P < 0.10$ for both eluxadoline groups vs placebo). Using the FDA response criteria for the full 12-week treatment period, patients receiving eluxadoline 100 and 200 mg (28.0 and 28.5%, respectively) had significantly improved composite scores compared to placebo (13.8%; $P = 0.002$ for both). There were no significant differences between placebo and eluxadoline regardless of dose when comparing WAP scores. Improvements in stool consistency scores in the eluxadoline 25- (16.8%; $P = 0.016$) and 200-mg (18.1%; $P = 0.008$) groups were noted relative to the placebo participants (8.2%).

At 12 weeks, only the 100-mg treatment group was significantly different relative to placebo for composite scores (20.2 vs. 11.3%; $P = 0.03$); however, neither of the individual components (WAP and stool consistency) were significant for the 100-mg group vs. placebo. Patients receiving eluxadoline 100 and 200 mg (63.5 and 59.3%, respectively) reported adequate relief overall during the study compared to placebo (46.4%; $P < 0.05$ for both).

The onset of effect in bowel function assessments was noted soon after treatment initiation, with largest differences from placebo generally occurring between two and three months of the study. Fewer daily bowel movements, incontinence episodes, and urgency episodes were reported in all groups during the study. Significant improvements were noted in IBS global symptom scores at weeks 8 and 12 in the 100- and 200-mg eluxadoline groups. Similarly, improvements in IBS QoL scores were seen in the 100- and 200-mg eluxadoline groups compared to placebo at weeks 4, 8, and 12. The use of loperamide and acetaminophen rescue medications was rare and similar in frequency across all treatment groups (average of less than one dose of loperamide per week). The study investigators concluded that the use of rescue

medications did not influence study results, but specific data were not reported.

A pair of concurrent multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 trials were conducted at sites in the United States, Canada, and the United Kingdom.[17] In total, 295 centers participated in the IBS-3001 trial and 241 centers participated in the IBS-3002 trial. The study consisted of a prescreening period of up to one week and a screening period of up to three weeks, followed by random assignment to a 26-week treatment with eluxadoline (75 or 100 mg) or placebo twice daily. In IBS-3001 trial, the treatment period was followed by a two-week follow-up period, but in the IBS-3002 trial treatment was followed by a four-week single-blind placebo withdrawal period. All patients were between 18 and 80 years of age with IBS-D diagnosed according to the Rome III criteria. Participants were enrolled if they had a mean WAP score of ≥3.0, a mean score of 5.5 on the Bristol Stool Scale with a score of >5 on at least five days, and an average IBS global symptom score of 2.0 or more. Patients receiving antidiarrheal, antispasmodic, or narcotic medications were excluded; however, participants maintained on antidepressants were allowed to participate provided that dosing had been stable for at least 12 weeks prior to enrollment. Loperamide 2 mg every 6 hours was allowed during the double-blind period, but the dose was capped at four doses per 24 hours and seven doses per 48 hours.

The primary efficacy end point was the percentage of patients who reported for at least half of all days that their WAP score was reduced from baseline by at least 30% and a Bristol Stool Scale score of <5 or had no bowel movement. In the event of no bowel movement any day, an improvement in WAP score of ≥30% was considered a sufficient response for that day. Patient responses were evaluated over 12 weeks (FDA end point) and 26 weeks (European Medicines Agency [EMA] end point). Secondary end points included pain relief (defined as WAP), improvements in stool consistency scores, adequate relief, and improvements in IBS–QoL questionnaire.

In the pooled analysis for weeks 1–12 (FDA end point), both the eluxadoline 75- (26.2%) and 100-mg (27.0%) treatment groups demonstrated significant improvements compared to placebo (16.7%; $P < 0.001$ for both comparisons). Similarly, for the EMA end point of the entire 26-week study period, eluxadoline 75- (26.7%) and 100-mg (31.0%) groups were significantly improved compared with participants receiving placebo (19.5%; $P < 0.001$ for both comparisons). Comparable responses were seen in both individual trials at both 12- and 26-week end points with the exception that the eluxadoline 75-mg (23.4%) group was not significantly different compared with placebo (19.0%) using the 26-week EMA end point in the IBS-3001 trial.

There was no significant improvement in WAP scores in either the IBS-3001 or IBS-3002 trials for either eluxadoline group compared with placebo. However, consistent statistical improvements in stool consistency scores, IBS-D global symptoms, and adequate relief of IBS symptoms were reported in both eluxadoline groups. Loperamide rescue was used in only 28% of patients, averaged less than one dose per week, and decreased after weeks 1–12. The results of the statistical analysis were nearly identical when the use of loperamide was considered as an indicator of nonresponse.

Safety

The most common adverse events in clinical trials included constipation, abdominal pain, and nausea in Phase 2 and Phase 3 trials of eluxadoline.[16,17] In a Phase 2 trial, adverse events occurred mostly in the 200-mg study group.[16] The incidence of constipation in the 200-mg study group was 10% and five patients discontinued therapy due to constipation (four in the 200-mg study group and one in the placebo group). In the 100-mg study group, 44% of patients experienced at least one adverse event with the top three being nausea (5%), headache (3%), and nasopharyngitis (4%). Other than nausea in the 200-mg study group (10%), all adverse events occurred less than 10% of the time in all dosage form groups (5, 25, 100, and 200 mg).

In the Phase 3 trials, 58% of patients in the 100-mg study group and 60% of patients in the 75-mg treatment group reported at least one adverse event with approximately 30% being GI related.[17] Serious adverse events were reported in 4.2% of the 75-mg study group, 4.8% of the 100-mg study group, and 3% of the placebo group. Constipation occurred in 8.6% of patients in the 100-mg group, but all of the constipation events were considered nonserious. Only 1.4% of patients discontinued eluxadoline due to constipation (across both the 75- and 100-mg study groups). Nausea and abdominal pain occurred in approximately 7% of 100-mg eluxadoline-treated patients (7.5 and 7.2%, respectively). Serious adverse events in the 100-mg study group included ischemic colitis (one event), respiratory failure (two events), stress cardiomyopathy (one event), and pancreatitis (five events including two in the 75-mg study group).

Four of the five cases of pancreatitis were associated with biliary sludge or excessive alcohol intake. The remaining case of pancreatitis and all eight cases of abdominal pain (defined as acute abdominal pain with abrupt elevations of liver enzymes) were associated with sphincter of Oddi spasm in study subjects without a gallbladder. Adverse events related to sphincter of Oddi spasm occurred most frequently within two weeks of eluxadoline initiation.

Current Place in Therapy

Eluxadoline was approved based on the results of Phase 2 and Phase 3 clinical trials. The Phase 3 trial included 26 weeks of treatment and a two- to four-week posttreatment follow-up. Experience with a longer duration of treatment has not been reported. It has not been compared to other drugs used to treat IBS-D in randomized clinical trials, but it is hypothesized that it may produce less constipation than loperamide which lacks

activity at the δ-opioid receptor. In clinical trials, eluxadoline improved symptoms (both the FDA end point and the EMA end point) compared to placebo and is an additional option for patients with IBS-D with symptoms unrelieved by other drugs. It is best reserved for patients who do not drink excessive alcohol and the dose should be reduced to 75 mg twice daily in patients who are unable to tolerate the 100-mg dose, without a gallbladder, receiving concomitant OATP1B1 inhibitors, or who have mild or moderate hepatic impairment. While loperamide rescue medication was rarely needed in eluxadoline clinical trials, studies investigating the combination of loperamide with eluxadoline in patients not achieving benefit with loperamide or eluxadoline alone would be beneficial. Likewise, it is also not clear how the concomitant use of antidepressants impacts eluxadoline in clinical practice. The clinical trial protocols allowed patients to continue antidepressant therapy if doses were stable prior to the study, but outcomes in this subset of patients were not reported in any of the trials.

Conclusion

IBS has a prevalence of 12% in North America with approximately one-third of patients having IBS-D in the United States. A variety of treatment options exist that alleviate one or more of the common IBS symptoms including abdominal pain and cramps, diarrhea, constipation, and bloating. These drugs include loperamide, antispasmodics, tricyclic antidepressants, alosetron, probiotics, and rifaximin but unfortunately not all patients benefit. The addition of newer agents and better study outcomes with the FDA IBS responder end point will hopefully increase effective treatment options for patients.

Eluxadoline is a μ-opioid receptor agonist and a δ-opioid receptor antagonist approved to treat adult patients with IBS-D. In clinical trials, eluxadoline improved symptoms (both the FDA end point and the EMA end point) compared to placebo. Additional studies investigating eluxadoline in combination with other drugs used to treat IBS-D would be beneficial.

Author Contributions

Conceived and designed the experiments: LSS, BLL. Analyzed the data: LSS, BLL. Wrote the first draft of the manuscript: LSS, BLL. Contributed to the writing of the manuscript: LSS, BLL. Agree with manuscript results and conclusions: LSS, BLL. Jointly developed the structure and arguments for the paper: LSS, BLL. Made critical revisions and approved final version: LSS, BLL. Both authors reviewed and approved of the final manuscript.

REFERENCES

1. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology*. 2012;143:1179–87.
2. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol*. 2012;10:712–21.
3. Guilera M, Balboa A, Mearin F. Bowel habit subtypes and temporal patterns in irritable bowel syndrome: systematic review. *Am J Gastroenterol*. 2005;313:940–58.
4. Singh P, Staller K, Barshop K, et al. Patients with irritable bowel syndrome-diarrhea have lower disease specific quality of life than irritable bowel syndrome-constipation. *World J Gastroenterol*. 2015;218:8103–9.
5. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA*. 2015;313:949–58.
6. Crowell MD, Harris L, Jones MP, Chang L. New insights into the pathophysiology of irritable bowel syndrome: implications for future treatments. *Curr Gastroenterol Rep*. 2005;7:272–9.
7. Sands BE. The placebo response rate in irritable bowel syndrome and inflammatory bowel disease. *Dig Dis*. 2009;27(suppl 1):68–75.
8. The US Food and Drug Administration. *Guidance for Industry Irritable Bowel Syndrome Clinical Evaluation of Drugs for Treatment*. The US Food and Drug Administration; 2012. Available at: http://www.fda.gov/downloads/Drugs/./Guidances/UCM205269.pdf. Accessed August 10, 2016.
9. Ford AC, Moayyedi P, Lacy BE, et al. Task force on the management of functional bowel disorders. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. *Am J Gastroenterol*. 2014;109:S2–26.
10. Weinberg DS, Smalley W, Heidelbaugh JJ, et al. American Gastroenterological Association Institute guideline on the pharmacological management of irritable bowel syndrome. *Gastroenterology*. 2014;147:1146–8.
11. Viberzi®[package insert]. Parsippany, NJ: Actavis Pharma Inc; 2015.
12. Drug Enforcement Administration, Department of Justice. Schedules of controlled substances: placement of eluxadoline into Schedule IV. *Fed Regist*. 2015;80(218):69861–4. [to be codified at 21 C.F.R. pt 1308].
13. Levy-Cooperman N, McIntyre G, Bonifacio L, et al. Abuse potential and pharmacodynamics characteristics of oral and intranasal eluxadoline, a mixed μ- and κ -opioid receptor agonist and γ-opioid receptor antagonist. *J Pharmacol Exp Ther*. September 19, 2016. doi: http://dx.doi.org/10.1124/jpet.116.236547.
14. Lacy BE. Emerging treatments in neurogastroenterology: eluxadoline a new therapeutic option for diarrhea-predominant IBS. *Neurogasteroenterol Motil*. 2016; 28:26–35.
15. Davenport JM, Covington P, Bonifacio L, et al. Effect of uptake transporters OAT3 and OATPIBI and efflux transporter MRP2 on the pharmacokinetics of eluxadoline. *J Clin Pharmacol*. 2015;55:534–42.
16. Dove LS, Lembo A, Randall CW, et al. Eluxadoline benefits patients with irritable bowel syndrome with diarrhea in a phase 2 study. *Gastroenterology*. 2013;145:329–38.
17. Lembo AJ, Lacy BE, Zuckerman MJ, et al. Eluxadoline for irritable bowel syndrome with diarrhea. *N Engl J Med*. 2016;374:242–53.