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Eluxadoline Benefits Patients With Irritable Bowel Syndrome With Diarrhea in a Phase 2 Study

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BACKGROUND & AIMS: Simultaneous agonism of the μ-opioid receptor and antagonism of the δ-opioid receptor can reduce abdominal pain and diarrhea in patients with irritable bowel syndrome with diarrhea (IBS-D) without constipating side effects. We evaluated the efficacy and safety of a minimally absorbed, μ-opioid receptor agonist and δ-opioid receptor antagonist (eluxadoline) in a phase 2 study in patients with IBS-D. **METHODS:** We randomly assigned 807 patients to groups that received oral placebo twice daily or 5, 25, 100, or 200 mg oral eluxadoline for 12 weeks. The primary end point was clinical response at week 4, defined by a mean reduction in daily pain score from baseline of ≥30%, and of at least 2 points on 0−10 scale, as well as a stool consistency score of 3 or 4 on the Bristol Stool Scale (1–7) for at least 66% of daily diary entries during that week. **RESULTS:** Significantly more patients receiving 25 mg (12.0%) or 200 mg (13.8%) eluxadoline met the primary end point of clinical response than patients given placebo (5.7%; $P < .05$). Patients receiving eluxadoline at 100 mg and 200 mg also had greater improvements in bowel movement frequency and urgency, global symptoms, quality of life, and adequate relief assessments ($P < .05$). Additionally, patients receiving 100 mg (28.0%) or 200 mg (28.5%) eluxadoline were significantly more likely than those receiving placebo (13.8%; $P < .005$) to meet the US Food and Drug Administration response end point during the full 12 weeks of the study. Eluxadoline was well tolerated with a low incidence of constipation. **CONCLUSIONS: In a phase 2 study of the mixed μ-opioid receptor agonist/δ-opioid receptor antagonist eluxadoline vs placebo in patients with IBS-D, patients given eluxadoline were significantly more likely to be clinical responders, based on a composite of improvement in abdominal pain and stool consistency. Further study of eluxadoline is warranted to assess its potential as a treatment for IBS-D. ClinicalTrials.gov number, NCT01130272**

Keywords: Clinical Trial; Functional Bowel Disorders; Transit; Drug.

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder that affects approximately 10%−15% of the population in Western countries.[1] IBS is characterized by recurrent abdominal discomfort and pain associated with altered bowel habits.[2] Currently, IBS subtypes are determined by stool consistency pattern and include diarrhea (IBS-D), constipation , or mixed constipation and diarrhea. IBS can negatively impact an individual's quality of life and results in significant direct and indirect costs.[3] Current safe and effective pharmacologic treatments for IBS-D are limited and include antispasmodics, antidepressants, antidiarrheal agents, and alosetron.[4]

Opioid receptors, including μ, δ, and κ, are expressed along the gastrointestinal tract and play a key role in regulating gastrointestinal motility, secretion, and visceral sensation.[5,6] Exogenous opioids reduce gastrointestinal transit through activation of μ-opioid receptor (MOR) and can treat diarrhea in acute situations.[7] Agents that simultaneously activate MOR and antagonize δ-opioid receptor (DOR) have differential gastrointestinal effects and can possess increased analgesic potency compared with pure MOR agonists.[8,9] Such a mixed MOR agonist/DOR antagonist profile can offer an advantage in treating both the diarrhea and abdominal pain associated with IBS-D.

Eluxadoline (nonproprietary name adopted by US Adopted Names Council; International Non-proprietary Name Committee pending) is a locally active, mixed MOR agonist/DOR antagonist with low oral bioavailability that is being developed for the treatment of IBS-D. In vitro, eluxadoline reduces contractility in intestinal tissue and inhibits neurogenically mediated secretion.[10] In vivo, eluxadoline reduces gastrointestinal transit and fecal output in stressed and nonstressed mice over a wide dose range without fully inhibiting gastrointestinal transit.[11] In contrast, loperamide had a narrow dose range in the same stressed and nonstressed models and completely prevented fecal output in a dose-dependent manner.[11] These data support the hypothesis that mixed MOR agonism/DOR antagonism can treat IBS-D without constipating side effects.

Abbreviations used in this paper: DOR, δ opioid receptor; EQ-5D, EuroQoL-5 Dimension; FDA, US Food and Drug Administration; GLMM, generalized linear mixed effects model; IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome with diarrhea; IBS-QOL, IBS-Quality of Life; IBS-SSS, IBS-Symptom Severity Score; IVRS, interactive voice response system; MOR, μ opioid receptor; WAP, worst abdominal pain.

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The safety and tolerability of single and multiple oral doses of eluxadoline were previously evaluated in a phase 1 study in healthy adults. This phase 2, proof-of-concept study evaluated the efficacy, safety, and tolerability of orally administered eluxadoline in patients with IBS-D.

Materials and Methods

Study Design

This phase 2 randomized, double-blind, placebo-controlled study enrolled patients from May 2010 until April 2011 at 263 primary and tertiary care centers within the United States. The trial was designed, conducted, and reported in compliance with the principles of Good Clinical Practice guidelines. An Institutional Review Board–approved informed consent was reviewed and signed by all patients before their participation in this trial.

This study consisted of an initial prescreening period, a screening period of 2 to 3 weeks, a 12-week double-blind treatment period, and a 2-week post-treatment period. During the 1-week prescreening period, patients underwent a physical examination, provided blood and urine for routine testing, and discontinued any prohibited medications. Patients who met the inclusion and exclusion criteria entered the screening period and began using an interactive voice response system (IVRS) to provide daily symptom assessments. After the screening period of 2–3 weeks, patients who continued to meet eligibility criteria and were compliant with the IVRS system for at least 6 of 7 days during the week before and 11 of 14 days during the 2 weeks before were randomized in parallel, 1:1:1:1:1 to receive placebo or eluxadoline 5, 25, 100, or 200 mg twice daily with breakfast and dinner. Randomization schedules were generated by an unblinded clinical research organization using the Plan procedure in SAS (version 9.1) with a minimum block size. The IVRS implemented the randomization, balancing sex across assigned treatment groups, and assigned the appropriate materials kit to the patient; site personnel dispensed the assigned materials. Patients returned for follow-up visits at weeks 2, 4, 8, and 12 and had a post-treatment assessment at week 14. All personnel involved in the design and implementation of the trial remained blinded until the database was locked, with the exceptions of the statisticians who generated the randomization schedule and the IVRS developers.

Daily IVRS measurements included worst abdominal pain (WAP), stool consistency, bowel frequency, rectal urgency, and frequency of stool incontinence. Weekly measurement included the IBS Global Symptom score on a 0–4 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe), where patients were asked "How would you rate your IBS symptoms overall over the past 7 days?" During monthly clinic visits, patients completed patient-reported outcomes questionnaires, including the IBS-Symptom Severity Score (IBS-SSS; scaled 0–500 with higher scores indicating more severe symptoms), IBS-quality of life (IBS-QOL; scaled 0–100 with higher scores indicating better quality of life), and EuroQoL-5 Dimension (EQ-5D; scaled 0–1 with lower scores indicating better quality of life) and answered the question "Over the past week have you had adequate relief of your IBS symptoms?" Safety assessments included capture of adverse events, clinical laboratory results, 12-lead electrocardiograms, vital signs, and physical examinations.

As an additional safety precaution, IVRS-generated notifications were sent to investigators to discontinue patients from the study for IVRS-confirmed constipation if the patients' diary entries indicated a lack of a bowel movement on 4 consecutive days on more than one occasion or the lack of a bowel movement on any 7 consecutive days (irrespective of whether an adverse event of constipation was reported). Additionally, the absence of diary entry on a given day was treated as the absence of a bowel movement by the IVRS; programmatic IVRS study withdrawal notifications were generated for patients that were noncompliant with the IVRS for the same criteria as the absence of a bowel movement.

Study Population and Sample Size

Eligible patients were male or female aged 18 to 65 years who met the Rome III criteria for IBS-D,[3] and who reported a mean daily WAP score of $\geq$3.0 (on a 0–10 numerical rating scale, where 0 indicates no pain and 10 worst pain imaginable) and mean daily stool consistency score of $\geq$5.5 on the Bristol Stool Scale (1 = hard, lumpy stools and 7 = watery, liquid stools) in the week before randomization. Patients were also required to have had a colonoscopy within the past 5 years for any alarm feature, such as weight loss, nocturnal symptoms, familial history of colon cancer, or blood mixed with stool. Patients with histories of inflammatory bowel disease, celiac disease, intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, fecal impaction, gastric banding, bariatric surgery, adhesions, ischemic colitis, impaired intestinal circulation, major vein thrombophlebitis, hypercoagulable states, major gastric, hepatic, pancreatic, or intestinal surgery, or evidence of significant hepatic or renal disease were excluded. Patients agreed to remain on a stable diet. Female patients of child-bearing potential agreed to use adequate birth control throughout the trial. Stable doses of medications for depression, migraine, anxiety, or other chronic conditions were permitted. However, antibiotics, anticholinergics, cholestyramine, cholinomimetics, opioids, colchicine, docusate, enemas, gastrointestinal preparations, 5-HT3 antagonists, and 5-HT4 agonists were required to be discontinued for at least 21 days before randomization. Nonsteroidal anti-inflammatory drugs used specifically for IBS symptoms were prohibited from 14 days before randomization.

Rescue Medication

Rescue medication was allowed after randomization to mitigate the potential for attrition or unwillingness to enter the study. Single-blind placebo rescue (weeks 1–4) followed by single-blind loperamide (2 mg/unit dosage, weeks 5–12) was allowed for uncontrolled diarrhea and acetaminophen was allowed for uncontrolled abdominal pain (weeks 1–12). Patients were withdrawn if they exceeded the maximum allowable dosages of antidiarrheal rescue, which were 4 unit doses in any 24-hour period, 7 unit doses in any 48-hour period, or 11 unit doses in any 7-day period.

Study Outcomes

The primary end point was the percentage of patients who achieved clinical response at week 4, defined as a patient who reported a decrease in the mean daily WAP scores from baseline by $\geq$30% and at least 2 points and a daily Bristol Stool Scale score of 3 or 4 on $\geq$66% of daily diary entries within that week.

Secondary end points included the percentage of patients who achieved clinical response at week 12 and the percentage of patients who achieved response to the individual WAP and stool consistency components at weeks 4 and 12. Other secondary and

exploratory end points included changes in bowel movement frequency, urgency, and incontinence, IBS Global Symptom score, IBS-SSS, IBS-adequate relief, and quality of life assessments based on the IBS-QOL and EQ-5D questionnaires.

After initiation of the study, the US Food and Drug Administration (FDA) issued recommendations for outcomes measures in IBS clinical trials. Consequently, after discussions with the FDA, post-hoc analyses were conducted based on the FDA recommended daily responder definition,[11] where patients were FDA responders if on at least 50% of days during the 12 weeks of the study their daily WAP score was reduced from baseline by $\geq$30% and they had either a daily Bristol Stool Scale score $<$5 or reported no bowel movement. FDA response was also assessed over each individual month of the study (ie, weeks 1−4, 5−8, and 9−12). Additionally, responses to the individual WAP and stool consistency components of the FDA response definition were assessed during the entire 12 weeks of the study and over each monthly interval as post-hoc analyses.

Statistical Analyses

The study was prospectively powered based on clinical response at week 4, assuming a response rate of 30% for at least one eluxadoline group and 15% for placebo. Assuming a 1-month dropout rate of 13%, 170 patients per group yields approximately 85% power comparing any single eluxadoline group to placebo using Fisher exact test with a 2-sided α-level of .05. Logistic models with covariates were assumed to have at least as much power as the Fisher exact test and so, for the a priori analyses, the 85% power was seen as a lower bound. An interim analysis was prospectively planned and executed by an independent interim analysis committee when approximately 85 patients per group had completed at least 4 weeks of treatment. No a priori stopping rules were developed, however, a prospective charter allowed the interim analysis committee to discontinue one or more arms based on safety, tolerability, lack of efficacy, or business considerations. Randomization would continue until approximately 170 patients were enrolled in each of the remaining groups.

The primary end point of clinical response was analyzed according to the final statistical analysis plan prospectively implemented before database lock and unblinding. Clinical response at weeks 4 and 12 was analyzed via a logistic regression using a generalized linear mixed effects model (GLMM) with center as a random effect and baseline WAP and stool consistency scores as covariates. Patients with $<$5 diary entries within week 4 or week 12 were categorized as nonresponders for that week. No imputation of data was performed if a diary entry was missed. Odds ratios from the logistic regressions were used to determine statistical significance of treatment effects as compared with placebo. The end points of bowel movement frequency, urgency episodes, and incontinence were modeled using a GLMM with fixed effects of treatment, time, and the treatment by time interaction; respective baseline frequencies were fitted in the model as baseline covariates. Additionally, a random effect was fit with patients as sampling units to account for repeated measurements of each outcome. Because outcomes were counts of events and likely non-normally distributed, the GLMMs were fit assuming a Poisson response distribution and a natural log link function.[12,13]

Other secondary and exploratory end points were modeled with similar GLMMs. IBS Global Symptom score was modeled as a normal response distribution (identity link) with fixed and random effects similar to count data, with the exception that the baseline covariate was not included because of not having collected a baseline assessment. IBS-SSS, IBS-QOL, and EQ-5D scores were modeled with fixed effects of treatment, time, and the treatment by time interaction, the baseline score, and a random effect to account for repeated measurements. The models for IBS-QOL and EQ-5D assumed a normal distribution and identity link. IBS-adequate relief was modeled like the IBS Global Symptom score (ie, with no baseline covariate), but assuming a binary distribution and logit link function.

The time metrics fit for the GLMM models reflected the frequency with which a given outcome variable was collected, for example, daily for bowel movements and weekly for global symptoms. Differences in GLMM model estimates were evaluated for statistical significance at days 28, 56, and 84 to summarize outcomes after 1, 2, and 3 months of treatment, respectively. Note that interpretation of treatment group effects for GLMMs depends on the link function used. Therefore, all models of binary outcomes result in effects that are odds ratios, count variable models result in risk ratios, and normally distributed variable models using the identity link function have the usual interpretation of effects being mean differences.

Post-hoc FDA response based on daily responder criteria—where patients must have met both WAP and stool consistency response criteria on a given day—was evaluated during the full 12-week interval and each monthly interval using a logistic regression model, controlling for baseline values of WAP, stool consistency scores, and bowel movement frequency. Minimal compliance criteria of 70% were required within the intervals analyzed; patients with $<$60 diary entries during the 12-week interval were categorized as nonresponders for the study and patients with $<$20 diary entries during any 4-week interval were categorized as nonresponders for that month. No imputation of data was performed if a diary entry was missed.

All authors had access to the study data and reviewed and approved the final manuscript.

Results

Participant Flow

Of the 807 patients randomized, 525 patients completed the trial and 282 discontinued treatment (Supplementary Figure 1). Reasons for discontinuation included 54 patients who were noncompliant with the daily IVRS, 43 patients who voluntarily withdrew, 42 patients who experienced adverse events, and 38 patients in the 5-mg eluxadoline group who discontinued when the treatment arm was deselected because of lack of efficacy. Discontinuations due to adverse events were more common among patients receiving 200 mg eluxadoline.

Eighteen patients were enrolled at a site terminated by Furiex for potential scientific misconduct identified during routine site auditing and were excluded from analysis. Of the remaining 789 patients randomized, 771 patients received at least 1 dose of study drug (safety set) and 754 received at least 1 dose of study drug and had at least 1 post-randomization assessment of the primary outcome (intent-to-treat set). Baseline characteristics in the intent-to-treat set were similar across groups, although patients in the 100-mg eluxadoline group had a slightly higher mean baseline pain score (Table 1). Patients averaged 4 to 5 bowel movements per day. More than 60% of patients

Table 1. Demographics and Baseline Characteristics (Intent-To-Treat Population)

Characteristic	Eluxadoline 5 mg (n = 105)	Eluxadoline 25 mg (n = 167)	Eluxadoline 100 mg (n = 163)	Eluxadoline 200 mg (n = 160)	Placebo (n = 159)
Age, mean (SD)	45.5 (12.9)	45.6 (11.9)	43.6 (10.9)	44.8 (11.7)	44.6 (12.5)
Male, n (%)	31 (30)	51 (31)	50 (31)	47 (29)	49 (31)
Female, n (%)	74 (70)	116 (69)	113 (69)	113 (71)	110 (69)
Pain, mean (SD)	5.8 (1.54)	5.9 (1.70)	6.1 (1.72)	5.8 (1.48)	5.9 (1.67)
Stool consistency, mean (SD)	6.2 (0.45)	6.2 (0.40)	6.2 (0.43)	6.2 (0.42)	6.2 (0.44)
BM frequency, mean (SD)	4.6 (2.47)	4.4 (3.16)	5.1 (3.59)	5.0 (3.21)	4.9 (3.57)
Urgency, mean (SD)	3.1 (1.96)	3.0 (2.92)	3.5 (3.32)	3.3 (2.33)	3.3 (3.15)
Incontinence, mean (SD)	1.1 (1.64)	0.9 (1.95)	1.1 (2.20)	0.9 (1.35)	1.1 (2.63)

NOTE. Baseline values represent daily averages for the 7 days before randomization for worst abdominal pain scores (on 0–10 numeric rating scale), stool consistency scores (on 1–7 Bristol Stool Scale), and daily averages for the number of daily bowel movements, and episodes of urgency and incontinence.
BM, bowel movement.

demonstrated baseline IBS-SSS means indicative of severe symptoms (ie, scores >300).[14]

Efficacy Results

Primary and secondary end points. Evaluating the prespecified primary end point at week 4 (Table 2), significantly more patients in the intent-to-treat population receiving 25 mg (12.0%; $P = .041$) and 200 mg eluxadoline (13.8%; $P = .015$) were clinical responders compared with placebo patients (5.7%). Although the 100-mg eluxadoline group did not achieve statistical significance at week 4, a similar trend for improvement over

Table 2. Primary and Secondary Efficacy Results: Clinical Response Criteria (Intent-to-Treat Population)

	Eluxadoline 5 mg (n = 105)	Eluxadoline 25 mg (n = 167)	Eluxadoline 100 mg (n = 163)	Eluxadoline 200 mg (n = 160)	Placebo (n = 159)
Primary end point					
Clinical response					
Week 4					
Composite, %	12.4[a]	12.0[b]	11.0[a]	13.8[b]	5.7
OR (95% CI)	2.46 (0.99–6.08)	2.38 (1.04–5.48)	2.08 (0.89–4.84)	2.80 (1.23–6.38)	
Abdominal pain, %	39.0	40.7	39.3	39.4	39.6
OR (95% CI)	1.06 (0.62–1.81)	1.08 (0.67–1.72)	0.99 (0.62–1.60)	1.02 (0.64–1.64)	
Stool consistency, %	12.4	16.8[b]	14.1[a]	18.1[b]	8.2
OR (95% CI)	1.58 (0.70–3.58)	2.38 (1.18–4.80)	1.90 (0.92–3.92)	2.61 (1.29–5.26)	
Secondary end points					
Clinical response					
Week 12					
Composite, %	8.6	13.2	20.2[b]	15.0	11.3
OR (95% CI)	0.72 (0.31–1.69)	1.21 (0.62–2.37)	2.01 (1.07–3.80)	1.40 (0.72–2.72)	
Abdominal pain, %	30.5	39.5	49.1[a]	36.3	39.6
OR (95% CI)	0.66 (0.39–1.14)	0.99 (0.63–1.56)	1.49 (0.94–2.34)	0.86 (0.54–1.37)	
Stool consistency, %	10.5	19.2	22.1[a]	20.0	15.1
OR (95% CI)	0.65 (0.30–1.41)	1.36 (0.75–2.47)	1.64 (0.91–2.94)	1.44 (0.79–2.61)	
Adequate relief response					
Week 4, n	103	163	156	150	153
Yes, %	59.1	62.4[a]	69.3[b]	67.4[b]	49.3
OR (95% CI)	1.49 (0.80–2.76)	1.71 (0.99–2.95)	2.32 (1.32–4.07)	2.12 (1.20–3.74)	
Week 8					
Yes, %	63.2	64.2[b]	74.9[b]	71.5[b]	53.1
OR (95% CI)	1.51 (0.90–2.55)	1.58 (1.01–2.47)	2.63 (1.66–4.18)	2.22 (1.38–3.57)	
Week 12					
Yes, %	67.0	65.9	79.7[b]	75.4[b]	56.8
OR (95% CI)	1.54 (0.69–3.44)	1.47 (0.76–2.83)	2.99 (1.49–6.00)	2.33 (1.13–4.82)	
Overall study					
%	50.5	55.2	63.5[b]	59.3[b]	46.4
OR (95% CI)	1.18 (0.71–1.94)	1.42 (0.91–2.22)	2.01 (1.27–3.16)	1.69 (1.07–2.66)	

NOTE. Response rates and odds ratios (OR) (95% confidence interval [CI]) are based on model estimates from the logistic regression with covariate adjustments included. Patients were considered responders if they met the clinical response definition for the composite of worst abdominal pain and stool consistency (or its individual pain and stool consistency parts), or if they answered "Yes" to the question "Over the past week have you had adequate relief of your IBS symptoms?" (Adequate Relief Response). Patients were considered an adequate relief responder for the overall study if they answered "Yes" for at least 2 of the 3 weeks. The numbers per group represent those for whom adequate relief was collected.
[a]$P < .10$ compared with placebo.
[b]$P < .05$ compared with placebo.

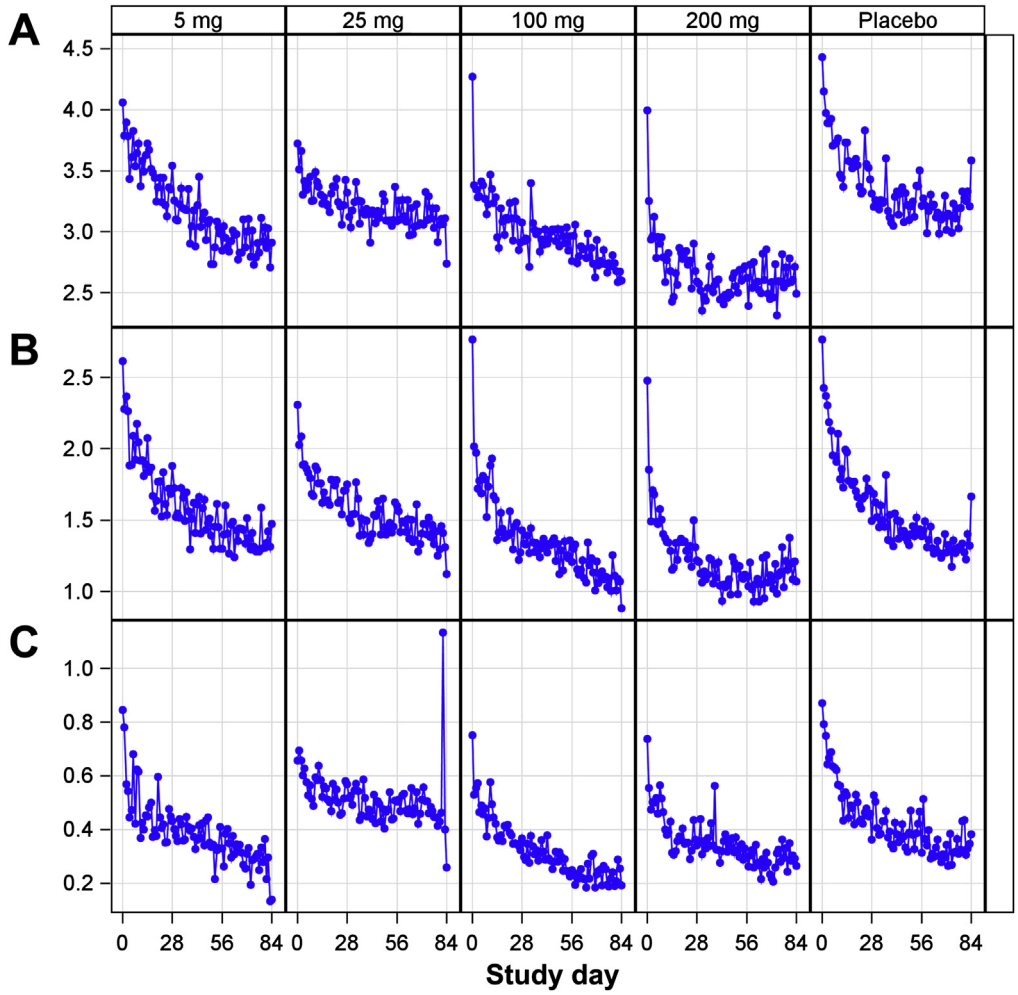

Figure 1. Bowel function assessments over time. Patient-reported averages plotted over time are presented for each active eluxadoline group vs placebo for (*A*) daily bowel movement frequency; (*B*) daily urgency episodes; and (*C*) daily incontinence episodes.

placebo was observed ($P = .090$). At week 12 (Table 2), a significantly greater percentage of patients receiving 100 mg eluxadoline (20.2%; $P = .030$) were clinical responders compared with placebo patients (11.3%). The 25-mg and 200-mg eluxadoline groups were not significantly different than placebo at week 12. Pain response rates at week 4 based on the WAP component of the clinical response definition were not different from placebo for any eluxadoline group (Table 2). A trend toward higher pain response rates was observed for the 100-mg eluxadoline group (49.1%; $P = .087$) compared with placebo (39.6%) at week 12. Stool consistency response rates at week 4 were significantly higher for the 25-mg (16.8%; $P = .016$) and 200-mg (18.1%; $P = .008$) eluxadoline groups compared with placebo (8.2%) with a similar trend observed for the 100-mg eluxadoline group (14.1%; $P = .083$). At week 12, a similar trend toward higher stool consistency response rates was seen for the 100-mg eluxadoline group (22.1%; $P = .098$) compared with placebo (15.1%). Rescue medication use for uncontrolled abdominal pain and diarrhea was uncommon and similar across all groups. Importantly, no difference in antidiarrheal rescue medication use was observed between the first month of the study and the last 2 months of the study. During both time periods, patients averaged <1 unit dose per week. Use of rescue medication for abdominal pain was even more rarely reported. Overall, use of rescue medication did not impact analyses of WAP, stool consistency, or composite response based on multiple sensitivity analyses (data not shown).

Patients treated with eluxadoline also reported experiencing adequate relief of their IBS symptoms to a greater extent than placebo patients (Table 2). Patients receiving 100 mg (odds ratios = 2.32, 2.63, and 2.99; $P = .004$, $P < .001$, and $P = .002$, respectively) and 200 mg (odds ratios = 2.12, 2.22, and 2.33; $P = .009$, $P = .001$, and $P = .023$, respectively) eluxadoline were more likely than placebo patients to report adequate relief of their IBS symptoms at weeks 4, 8, and 12. Likewise, a significantly greater percentage of patients receiving 100 mg (63.5%, odds ratio = 2.01; $P = .003$) and 200 mg (59.3%, odds ratio = 1.69; $P = .025$) eluxadoline reported adequate relief of their IBS symptoms on at least 2 of the 3 monthly assessments compared with placebo patients (46.4%).

Decreasing counts for daily bowel movements, urgency episodes, and incontinence episodes were observed for all groups during the 3 months of treatment. The onset of the effect was rapid from the start of dosing for all bowel measurements, with differences from placebo generally reaching peak effects between the second and third months (Figure 1).

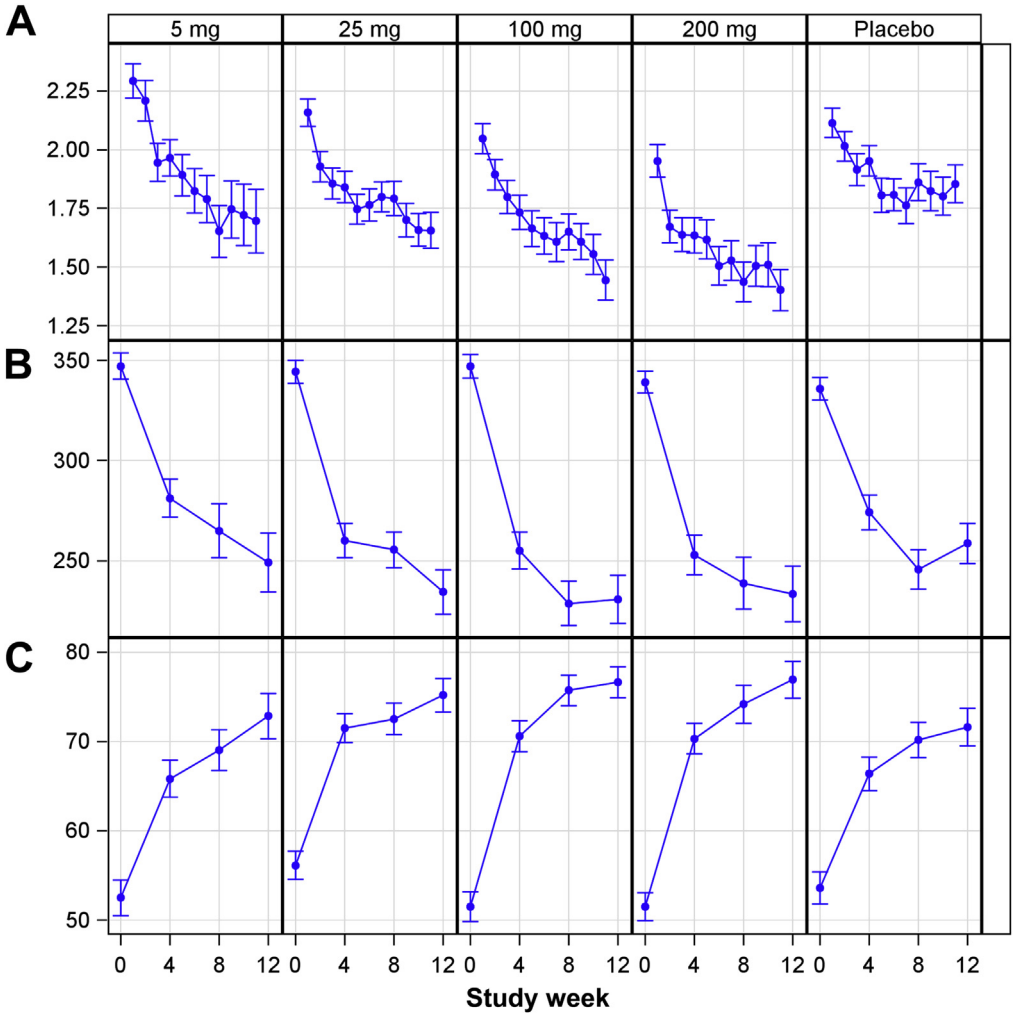

Figure 2. Global Symptom assessments and quality of life measures over time. Patient-reported averages plotted over time are presented for each active eluxadoline group vs placebo for: (*A*) weekly IBS Global Symptom score; (*B*) monthly IBS-SSS; and (*C*) monthly IBS-QOL. Error bars represent ±1 SEM.

Compared with placebo, relative risk estimates for bowel movements for patients receiving 100 and 200 mg eluxadoline were 0.88 ($P = .006$) and 0.78 ($P < .001$), 0.88 ($P = .011$) and 0.80 ($P < .001$), and 0.89 ($P = .022$) and 0.82 ($P < .001$) at days 28, 56, and 84, respectively. Likewise, relative risk estimates for urgency episodes for patients receiving 100 and 200 mg eluxadoline were 0.74 ($P = .008$) and 0.65 ($P < .001$), 0.76 ($P = .013$) and 0.67 ($P < .001$), and 0.77 ($P = .024$) and 0.69 ($P = .002$) at days 28, 56, and 84, respectively. No significant differences from placebo in incontinence episodes were observed. However, a trend for improvements in incontinence-free days was noted for patients who averaged at least 1 incontinent episode per day in the week before randomization (38.8 vs 26.5 incontinence-free days for 100-mg eluxadoline patients compared with placebo patients, respectively; $P = .078$). Although changes over time in abdominal pain and stool consistency were only analyzed via the response definitions specified in the primary and secondary end points, reductions from baseline values followed a similar time course to those shown for the other bowel characteristics (data not shown). During the 2-week follow-up period after week 12, values for abdominal pain, stool consistency, and bowel characteristics began to increase for all treatment groups, but remained below baseline levels.

Consistent improvement during the course of the study was also seen in patients' ratings of their global IBS symptoms, with peak effects again observed between the second and third months (Figure 3). For IBS Global Symptom scores, mean differences from placebo were statistically significant for patients receiving 200 mg eluxadoline (−0.26; $P < .001$) at week 4 and for both the 100-mg (−0.19 and −0.26; $P = .014$ and 0.003, respectively) and 200-mg (−0.30 and −0.34; $P < .001$ and $< .001$, respectively) eluxadoline groups at weeks 8 and 12. Likewise for IBS-SSS, mean differences from placebo were statistically significant for the 100-mg eluxadoline group at the end of weeks 4, 8, and 12 (−16.69, −33.55, and −50.40; $P = .011$; $P < .001$; and $P < .001$, respectively) and for the 200-mg eluxadoline group at the end of weeks 8 and 12 (−19.89 and −27.48; $P = .012$ and $P = .011$, respectively). Patients who received eluxadoline also reported significant improvement in their quality of life (Figure 2). A greater improvement in IBS-QOL total scores was observed for patients receiving 100 mg and 200 mg eluxadoline compared with placebo at the end of weeks 4, 8, and 12. For patients receiving 100 mg eluxadoline, mean differences from placebo were 3.05 ($P = .012$), 5.82 ($P < .001$), and 8.60 ($P < .001$). For patients receiving 200

Table 3. Post-Hoc Efficacy Results: FDA Response Criteria (Intent-to-Treat Population)

	Eluxadoline				
	5 mg (n = 105)	25 mg (n = 167)	100 mg (n = 163)	200 mg (n = 160)	Placebo (n = 159)
FDA response (full study)					
Weeks 1–12					
Composite, %	13.3	16.9	28.0[a]	28.5[a]	13.8
90% CI	0.96 (0.47–1.95)	1.28 (0.70–2.32)	2.43 (1.38–4.28)	2.50 (1.42–4.40)	
Abdominal pain, %	34.8	46.7	55.2[a]	46.6	43.9
90% CI	0.68 (0.41–1.14)	1.12 (0.72–1.74)	1.57 (1.01–2.45)	1.11 (0.72–1.73)	
Stool consistency, %	20.1	21.4	33.4[b]	36.9[a]	23.8
90% CI	0.80 (0.44–1.46)	0.87 (0.52–1.46)	1.60 (0.98–2.62)	1.86 (1.14–3.04)	
FDA response (by month)					
Weeks 1–4, n	105	167	163	160	159
Composite, %	10.8	14.3	21.1	23.7[b]	15.8
90% CI	0.65 (0.31–1.35)	0.89 (0.49–1.63)	1.43 (0.81–2.52)	1.66 (0.95–2.91)	
Abdominal pain, %	39.4	44.9	44.8	42.7	41.9
90% CI	0.90 (0.54–1.49)	1.13 (0.73–1.76)	1.13 (0.72–1.76)	1.03 (0.66–1.61)	
Stool consistency, %	20.5	22.3	30.6[a]	38.6[a]	20.2
90% CI	1.02 (0.55–1.87)	1.13 (0.67–1.93)	1.74 (1.04–2.90)	2.48 (1.50–4.11)	
Weeks 5–8, n	90	146	137	125	139
Composite, %	26.9	23.3	37.8[a]	40.2[a]	21.8
90% CI	1.32 (0.71–2.45)	1.09 (0.62–1.91)	2.18 (1.28–3.72)	2.41 (1.40–4.15)	
Abdominal pain, %	53.1	58.4	64.5	59.1	59.7
90% CI	0.76 (0.45–1.31)	0.95 (0.59–1.52)	1.22 (0.75–1.99)	0.97 (0.59–1.60)	
Stool consistency, %	30.4	28.8	45.9[a]	47.4[a]	30.3
90% CI	1.00 (0.56–1.79)	0.93 (0.56–1.56)	1.95 (1.19–3.21)	2.07 (1.25–3.44)	
Weeks 9–12, n	72	137	129	109	126
Composite, %	22.6	30.3	44.3[a]	46.3[a]	25.5
90% CI	0.85 (0.43–1.68)	1.27 (0.74–2.20)	2.33 (1.37–3.98)	2.52 (1.45–4.40)	
Abdominal pain, %	45.4	56.5	71.0[a]	68.8[b]	56.2
90% CI	0.65 (0.36–1.16)	1.01 (0.62–1.65)	1.90 (1.13–3.20)	1.71 (1.00–2.94)	
Stool consistency, %	25.5	35.1	48.2[a]	56.6[a]	32.5
90% CI	0.71 (0.37–1.36)	1.13 (0.67–1.89)	1.93 (1.16–3.23)	2.71 (1.58–4.64)	

NOTE. Response rates and odds ratios (OR) (90% confidence intervals [CI]) are based on model estimates from the logistic regression with covariate adjustments included. Patients were considered responders if they met the FDA daily responder definition for the composite of worst abdominal pain and stool consistency (or its individual pain and stool consistency parts) for at least 50% of time over the interval from weeks 1–12 or over each monthly interval. Patients were included in a monthly interval if they received at least one dose of study medication within that interval.

[a] $P < .05$ compared with placebo.

[b] $P < .10$ compared with placebo.

mg eluxadoline, mean differences were 3.31 ($P = .007$), 5.75 ($P < .001$), and 8.19 ($P < .001$) at the end of weeks 4, 8, and 12. Results from the EQ-5D questionnaire also revealed a statistically significant difference ($P < .001$) from placebo for patients in the 100-mg eluxadoline group at both weeks 8 and 12; however, mean EQ-5D results for all groups remained within normal ranges for the population throughout the course of the study.

FDA end points. In the post-hoc analysis of the FDA end point, FDA response rates during the full 12-week interval were statistically superior for patients receiving 100 mg (28.0%; $P = .002$) and 200 mg (28.5%; $P = .002$) eluxadoline compared with placebo (13.8%) (Table 3); patients receiving eluxadoline at 100 mg and 200 mg were more than twice as likely as placebo patients to be responders. A significantly higher pain response based on the WAP component of the FDA response definition was also seen for the 100-mg eluxadoline group (55.2%; $P = .045$) compared with placebo (43.9%). Stool consistency response based on the stool consistency component of the FDA response definition was significantly higher for patients receiving 200 mg eluxadoline (36.9%; $P = .013$) compared with placebo (23.8%), with a similar trend observed for 100-mg eluxadoline patients (33.4%; $P = 0.059$). Post-hoc monthly analyses during the intervals from weeks 1–4, 5–8, and 9–12 showed a consistently durable effect for overall FDA response, with rates for patients receiving 100 mg and 200 mg eluxadoline being statistically superior to placebo over the latter 2 intervals (Table 3).

Safety and Tolerability

Adverse event rates were similar across all groups and showed no obvious dose-dependent trend from 5 mg to 100 mg; however, patients in the 200-mg eluxadoline group reported higher rates of severe events, adverse events leading to discontinuation, and nonserious gastrointestinal and central nervous system events (Table 4). The most common gastrointestinal events reported were nausea, abdominal pain, vomiting, and constipation—the majority showing the highest rates in the 200-mg eluxadoline group. Although the rate of constipation was highest for the 100-mg eluxadoline group, none of the adverse events of constipation reported by these patients led to discontinuation or was rated severe in intensity. A total of 5 adverse events of patient-reported

Table 4. Most Commonly Reported Treatment-Emergent Adverse Events (Safety Population)

	Eluxadoline				
	5 mg (n = 105)	25 mg (n = 170)	100 mg (n = 165)	200 mg (n = 172)	Placebo (n = 159)
At least 1 TEAE	46 (44)	86 (51)	73 (44)	90 (52)	78 (49)
Nausea	6 (6)	11 (6)	9 (5)	18 (10)	7 (4)
Headache	3 (3)	12 (7)	5 (3)	7 (4)	6 (4)
Nasopharyngitis	4 (4)	8 (5)	7 (4)	6 (4)	6 (4)
Abdominal pain	3 (3)	6 (4)	4 (2)	13 (8)	3 (2)
Dizziness	4 (4)	4 (2)	5 (3)	11 (6)	4 (3)
Vomiting	1 (1)	7 (4)	7 (4)	12 (7)	1 (1)
Constipation	2 (2)	5 (3)	10 (6)	6 (3)	4 (3)

NOTE. Values are n (%).
TEAC, treatment-emergent adverse event.

constipation led to study drug discontinuation, 4 in the 200-mg eluxadoline group and 1 in the placebo group. Four patients discontinued from the study because of IVRS-confirmed constipation; 2 of these 4 patients also reported adverse events of constipation (which did not contribute to discontinuation) coincident to the IVRS data (one each in the 25-mg and 100-mg eluxadoline groups). No serious adverse events of constipation were reported.

Three serious adverse events of pancreatitis were reported by patients during treatment with eluxadoline (2 at 200 mg and 1 at 25 mg). The 2 pancreatitis events at 200 mg occurred within the first 2 doses of study medication and the event at 25 mg occurred after 18 days of twice daily dosing; all resolved rapidly without sequelae. Among these 3 cases, one 200-mg event was confounded by a documented blood alcohol level of 76 mg/dL at the time of the event and a recent hospitalization for alcoholic pancreatitis 2 months before study entry. A fourth case of pancreatitis, which was also transient in nature, occurred approximately 15 days after the patient's last dose of 100 mg eluxadoline; this event occurred when the patient was being treated for bronchitis with clarithromycin. All 4 cases of pancreatitis were unblinded on the reporting of this last case and were determined to have occurred in the eluxadoline treatment arms.

Results from routine laboratory evaluations, vital sign measurements, physical examinations, and electrocardiograms were unremarkable and revealed no treatment-related effects.

Discussion

Eluxadoline is a mixed MOR agonist/DOR antagonist under development as a potential treatment for IBS-D. Although centrally acting mixed MOR agonist/DOR antagonist compounds have been investigated for potential analgesic advantages over pure MOR agonists, eluxadoline is being evaluated specifically for its peripheral effects because it has very low bioavailability when administered orally.[11] In animal models of altered gastrointestinal function, eluxadoline has demonstrated the ability to normalize fecal output over a wide dose range without completely blocking gastrointestinal transit, unlike the pure MOR agonist loperamide.[11] These data provide the rationale to evaluate the effectiveness of eluxadoline to treat the symptoms of IBS-D. In this phase 2 clinical trial, eluxadoline treatment resulted in statistically significantly greater percentages of patients with IBS-D who met the primary end point of clinical response at week 4 compared with placebo treatment.

All response rates for the primary end point were modest, despite odds ratios for eluxadoline groups exceeding 2 when compared with placebo (results statistically significant for 25 mg and 200 mg eluxadoline). These overall low response rates for the primary end point might be primarily attributable to the composite nature of the clinical response definition, namely the requirement that a patient meet the prespecified improvements in both worst abdominal pain and stool consistency in the same week. Patients had to first be dichotomized as either responders or nonresponders for each of the individual components of the composite, and only if they were responders for both were they categorized as a clinical responder. The combination of these 2 dichotomous criteria was therefore quite restrictive and appears to be overburdened by the more discriminatory of the 2, specifically the requirement to meet a stool consistency score of 3 or 4 on at least 2 of 3 of the daily diary entries in a week. When evaluating week 4 response rates for the individual components of the composite response definition, eluxadoline treatment yielded abdominal pain responses of approximately 40% across groups (not significantly different from placebo) and stool consistency responses of <20% (statistically significant for 25 mg and 200 mg eluxadoline). The latter response rates (ie, stool consistency response) are more consistent with those of the composite response and appear to drive the low overall response rates for the primary end point.

The rigor of the composite is further illustrated by the very low placebo response reported for the primary end point; this stands in contrast to the well-documented high placebo response in IBS.[15] A recent meta-analysis of randomized clinical trials in IBS suggests a mean placebo response rate of approximately 40% based on various global response criteria, including binary outcomes such as patients' subjective assessments of relief.[16] In the present study, placebo responses rates for the secondary end point of adequate relief of IBS symptoms were more consistent with the historical rates, with values of approximately 50%

at each monthly assessment. Importantly, the treatment effects for eluxadoline were more robust when assessed by this measure, with patients treated at 100 mg and 200 mg significantly more likely than placebo patients to perceive that their IBS symptoms were adequately relieved (odds ratios >2 for all 3 monthly assessments).

The treatment effects of eluxadoline appeared to increase with time on treatment. Although only significant over placebo for the 100-mg eluxadoline group, response rates based on the protocol-specified composite were greater for all treatment groups at week 12 than at the time of the primary end point at week 4. Effects for the secondary end points of bowel movement frequency, urgency, global symptom scores, and quality of life followed a similar time course, with maximal improvements over placebo generally observed between the second and third month of treatment. However, a higher degree of variability in the data collected during the latter part of the study (as shown in Figures 2 and 3) precludes any definitive conclusion on whether the effects of eluxadoline might regress after 2 to 3 months of treatment or if the effect persists with continued treatment. This will need to be evaluated in future studies of longer duration. Importantly, data collected during the 2-week follow-up period in this study revealed no rebound worsening for any of the secondary end point measures after stopping treatment.

As a supplemental evaluation of efficacy, post-hoc analyses were conducted in accordance with the end-point recommendation of the FDA guidance on IBS.[12] Although the nature of the primary end point specified in the protocol was consistent with the recommendations of the FDA (ie, a composite of improvement in pain and stool consistency), it differs from the suggested FDA end point by evaluating clinical response only during the 7 days of week 4 rather than during the entire 12 weeks of treatment. By contrast, the post-hoc FDA analyses encompassed all 12 weeks of efficacy data and required responders to achieve daily improvements in abdominal pain and stool consistency for at least 50% of time on study. In those analyses, FDA composite response rates for both the 100-mg and 200-mg eluxadoline groups were significantly greater than placebo (odds ratios >2) and demonstrated a more discernible dose-response pattern than did the primary end-point analysis. Post-hoc FDA response for abdominal pain was significantly greater than placebo for the 100-mg eluxadoline group, and stool consistency response displayed a more dose-proportional response with superiority over placebo observed for the 200-mg eluxadoline group ($P < .10$ for the 100-mg eluxadoline group). The higher dropout rate in the 200-mg eluxadoline group and lack of data imputation for those dropouts may contribute to the failure of that dose to achieve superiority over placebo for the pain responses during the 12-week study interval used in the post-hoc analyses.

The most common adverse events reported were those of the gastrointestinal system. Gastrointestinal adverse events, including nausea, vomiting, and abdominal pain, were more frequently reported in the 200-mg eluxadoline group, suggestive of a continuum of eluxadoline's local pharmacological effects on the gut. The higher incidence of abdominal pain reported in the 200-mg eluxadoline group might also contribute to the lack of efficacy seen for pain response in this dose group. Although the incidence rate of constipation was higher in the 100-mg eluxadoline group, the events were generally mild in intensity and were tolerated by the patients without requiring discontinuation of study drug. The most notable safety finding among patients receiving eluxadoline was infrequent reports of pancreatitis, including 2 cases that occurred after only 1 or 2 doses of study drug. Although 2 of the 4 total pancreatitis cases were confounded by mitigating factors (one patient with high blood alcohol level at the onset of the event and another patient who was off study drug for 2 weeks at the onset of the event), a possible relationship to eluxadoline treatment could not be ruled out because of the known association between opioids and acute pancreatitis and the lack of any such events among placebo-treated patients in this study.[17] After the last case, the protocol was amended to exclude patients who might have been predisposed to pancreatitis, that is, those with histories of pancreatitis, biliary duct disease, sphincter of Oddi dysfunction, alcohol abuse, binge drinking, elevated serum lipase, or cholecystectomy. The rationale for excluding patients with sphincter of Oddi dysfunction was based on the knowledge that patients experiencing sphincter of Oddi dysfunction are sensitive to opioids and can experience severe abdominal pain and pancreatitis, even after a single dose of opioid-containing medications.[18] Importantly, after implementation of the amendment, no additional events of pancreatitis were reported among the 210 patients enrolled. Future studies will need to prospectively evaluate the potential association between pancreatitis and eluxadoline treatment and also evaluate whether the exclusionary precautions implemented in the current study might minimize any potential risk.

Overall, the results from the current study confirm the effectiveness of eluxadoline to manage IBS-D based on a composite response of abdominal pain and stool consistency without significant risk of constipation. These results also suggest that additional clinical development of eluxadoline is warranted to validate the clinical meaningfulness of the composite end point and to determine what baseline patient characteristics are predictive of clinical response with eluxadoline.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2013.04.006.

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Conflicts of interest

These authors disclose the following: Leonard S. Dove is an employee of Furiex Pharmaceuticals and owns options of the company. Anthony Lembo is a consultant to Ironwood, Prometheus, and Salix. Charles W. Randall is a consultant to Furiex, Prometheus, and Salix. David Andrae, J. Michael Davenport, Gail McIntyre, June S. Almenoff, and Paul S. Covington are employees of Furiex Pharmaceuticals and own shares and/or options of the company. The remaining author discloses no conflicts.

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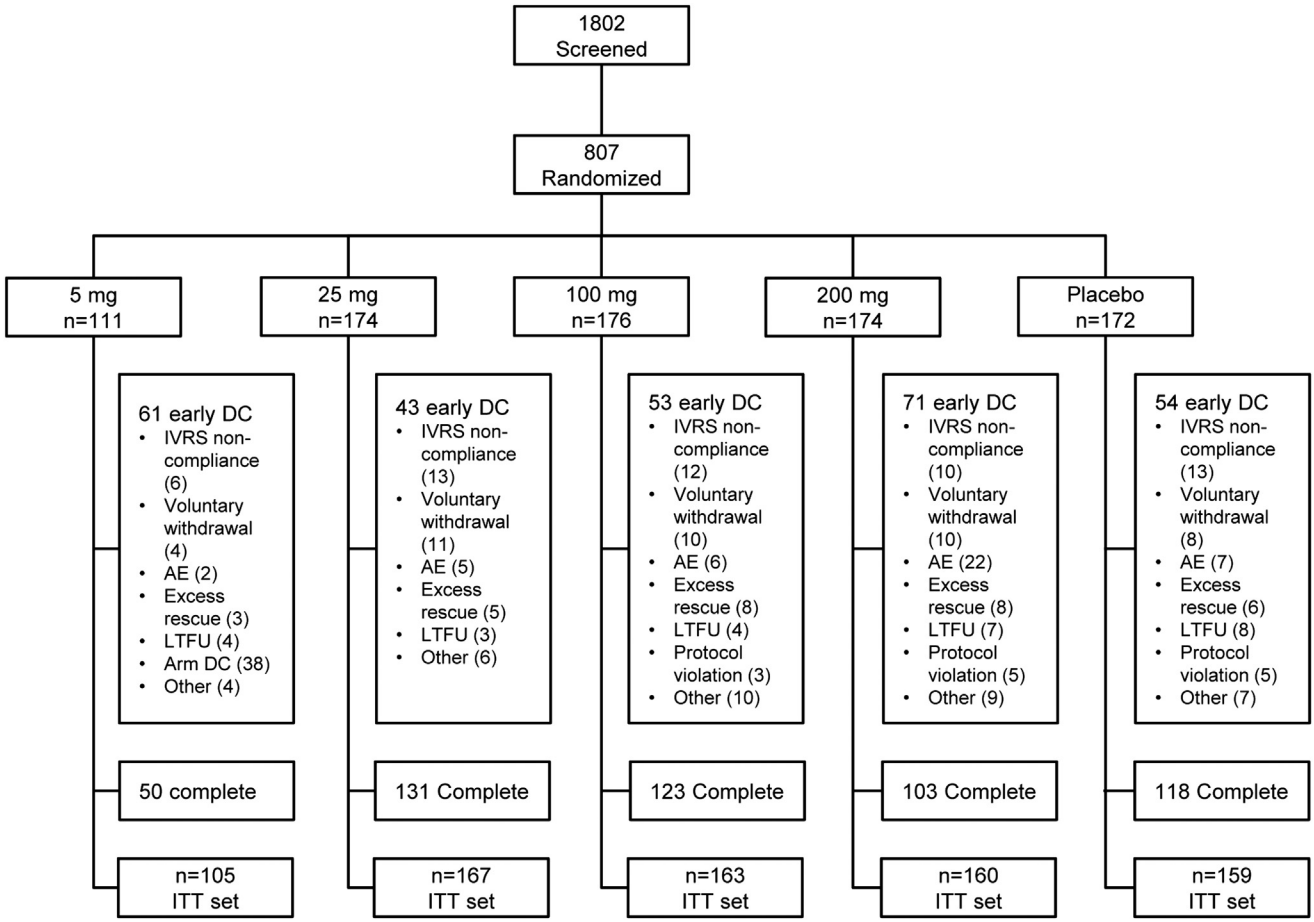

Supplementary Figure 1. Patient disposition. The "other" category includes IVRS-confirmed constipation, lack of efficacy, physician decision, and sponsor decision; AE, adverse event, DC, discontinued, ITT, intent-to-treat, IVRS, interactive voice response system, LTFU, lost to follow-up.