ORIGINAL ARTICLE

Eluxadoline for Irritable Bowel Syndrome with Diarrhea

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ABSTRACT

BACKGROUND

Effective and safe treatments are needed for patients who have irritable bowel syndrome (IBS) with diarrhea. We conducted two phase 3 trials to assess the efficacy and safety of eluxadoline, a new oral agent with mixed opioid effects (μ- and κ-opioid receptor agonist and δ-opioid receptor antagonist), in patients with IBS with diarrhea.

METHODS

We randomly assigned 2427 adults who had IBS with diarrhea to eluxadoline (at a dose of 75 mg or 100 mg) or placebo twice daily for 26 weeks (IBS-3002 trial) or 52 weeks (IBS-3001 trial). The primary end point was the proportion of patients who had a composite response of decrease in abdominal pain and improvement in stool consistency on the same day for at least 50% of the days from weeks 1 through 12 and from weeks 1 through 26.

RESULTS

For weeks 1 through 12, more patients in the eluxadoline groups (75 mg and 100 mg) than in the placebo group reached the primary end point (IBS-3001 trial, 23.9% with the 75-mg dose and 25.1% with the 100-mg dose vs. 17.1% with placebo; P=0.01 and P=0.004, respectively; IBS-3002 trial, 28.9% and 29.6%, respectively, vs. 16.2%; P<0.001 for both comparisons). For weeks 1 through 26, the corresponding rates in IBS-3001 were 23.4% and 29.3% versus 19.0% (P=0.11 and P<0.001, respectively), and the corresponding rates in IBS-3002 were 30.4% and 32.7% versus 20.2% (P=0.001 and P<0.001, respectively). The most common adverse events associated with 75 mg of eluxadoline and 100 mg of eluxadoline, as compared with placebo, were nausea (8.1% and 7.5% vs. 5.1%), constipation (7.4% and 8.6% vs. 2.5%), and abdominal pain (5.8% and 7.2% vs. 4.1%). Pancreatitis developed in 5 (2 in the 75-mg group and 3 in the 100-mg group) of the 1666 patients in the safety population (0.3%).

CONCLUSIONS

Eluxadoline is a new therapeutic agent that reduced symptoms of IBS with diarrhea in men and women, with sustained efficacy over 6 months in patients who received the 100-mg dose twice daily. (Funded by Furiex Pharmaceuticals, an affiliate of Allergan; IBS-3001 and IBS-3002 ClinicalTrials.gov numbers, NCT01553591 and NCT01553747, respectively.)

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The irritable bowel syndrome (IBS) with diarrhea is a common functional gastrointestinal disorder that is characterized by recurring abdominal pain, bloating, and loose, frequent stools in the absence of structural, inflammatory, or biochemical abnormalities. IBS with diarrhea is associated with impairment in health-related quality of life, places a considerable financial burden on society because of reduced work productivity, and increases the use of health-related resources.[1,2] IBS is the most frequent diagnosis in gastroenterology practices and one of the most frequent diagnoses in primary care practices.[3]

Current treatment options for IBS with diarrhea are limited. Initial therapies include dietary and lifestyle modifications along with antidiarrheal agents; these therapies are frequently unsuccessful. A subgroup of patients with IBS with diarrhea may have a response to either rifaximin or alosetron.[4,5] Alosetron has been approved by the Food and Drug Administration (FDA) only for women with severe IBS with diarrhea who have not had a response to conventional therapy, although subsequent data suggest efficacy in men.[6,7]

Opioid receptors (including μ-, δ-, and κ-opioid receptors) in the enteric circuitry of the gastrointestinal tract play a role in regulating gastrointestinal motility, secretion, and visceral sensation. The mechanism of action of opioid agonists is complex because of various receptor subtypes and various sites of action (central sites vs. peripheral sites), but these agents are generally mediated through inhibitory effects that interrupt neuroneuronal and neuroeffector transmission.[8] The effects of activation of μ-opioid receptors on gastrointestinal motility and secretion have been studied more extensively than the effects of activation or modulation of δ-opioid receptors and κ-opioid receptors.

The δ-opioid receptors are expressed in overlapping neuronal populations, and their agonists have been shown to inhibit effects on gastrointestinal circular muscle.[9] Antagonism of δ-opioid receptors has been shown to functionally counteract the inhibiting effects of μ-opioid receptor agonists on gastrointestinal transit and increase μ-opioid receptor–mediated central analgesia.[10-12]

Eluxadoline (Viberzi, Allergan) is a peripherally acting mixed μ-opioid receptor agonist–δ-opioid receptor antagonist and κ-opioid receptor agonist with minimal oral bioavailability.[12] Nonclinical studies have shown that, unlike selective μ-opioid receptor agonists, eluxadoline reduces visceral hypersensitivity without completely disrupting intestinal motility. These data suggest that peripheral δ-opioid receptor antagonism may reduce μ-opioid receptor–mediated constipation and, similar to its documented effects on central analgesia, enhance μ-opioid receptor–mediated peripheral analgesia.[12]

In a phase 2 study, a significantly greater proportion of patients who received eluxadoline at a dose of 100 mg or 200 mg twice daily than of patients who received placebo reported reductions in their symptoms of IBS with diarrhea.[13] Since the 200-mg twice-daily dose did not provide efficacy advantages over the 100-mg dose and resulted in more adverse events, phase 3 trials included a group of patients who received a dose of 100 mg twice daily and a group of patients who received 75 mg twice daily. The objectives of these current trials were to evaluate the clinical response of patients with IBS with diarrhea to eluxadoline, as compared with placebo, through 26 weeks and to evaluate the safety of eluxadoline up to 52 weeks.

Methods

Patients

We enrolled patients who were 18 to 80 years of age and who had IBS with diarrhea (as assessed according to the Rome III diagnostic criteria for IBS).[14] Enrolled patients were included if they recorded, during the week before randomization, an average score for their worst abdominal pain as greater than 3.0 (on a scale of 0 to 10, with 0 indicating no pain and 10 the worst imaginable pain), an average score for stool consistency of 5.5 or more on the Bristol Stool Form Scale (which ranges from 1 to 7, with 1 indicating hard stool and 7 indicating watery diarrhea), a score of 5 or higher on the Bristol Stool Form Scale for at least 5 days, and an average IBS-D global symptom score for symptoms of IBS with diarrhea of 2.0 or more (on a scale of 0 to 4, with 0 indicating no symptoms of IBS with diarrhea and 4 very severe symptoms of IBS with diarrhea).

Patients were excluded if they had a history of inflammatory bowel disease or celiac disease, abnormal thyroid function, a history of alcohol

abuse[15] or binge drinking,[16] pancreatitis, sphincter of Oddi dysfunction, post-cholecystectomy biliary pain, cholecystitis within the past 6 months, or a known allergy to opioids, or if they were pregnant or breast-feeding or were receiving antidiarrheal, antispasmodic, or narcotic drugs. Patients who were receiving antidepressant medications were eligible to participate in the study, provided that dosing had been stable for 12 weeks or longer before enrollment.

STUDY DESIGN

We conducted two randomized, double-blind, placebo-controlled, parallel-group, multicenter studies from May 29, 2012, through July 29, 2014. A total of 295 centers participated in the IBS-3001 trial (269 in the United States, 9 in Canada, and 17 in the United Kingdom). This total included 40 IBS-3002 sites that agreed to participate in the IBS-3001 trial once enrollment was completed in the IBS-3002 trial. From May 29, 2012, through January 9, 2014, a total of 261 centers participated in the IBS-3002 trial (241 in the United States, 10 in Canada, and 10 in the United Kingdom).

The studies included a pretreatment period (a prescreening period of up to 1 week and a screening period of up to 3 weeks) and a 26-week double-blind, placebo-controlled study period for collection of efficacy data. This period was followed by either 26 additional weeks of double-blind treatment for safety assessment only and a 2-week post-treatment follow-up period (IBS-3001) or a 4-week, single-blind period of placebo withdrawal (i.e., regardless of original randomization, all patients received single-blind placebo to assess for rebound worsening of symptoms) (IBS-3002) (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Patients who met the inclusion criteria and did not meet exclusion criteria were randomly assigned to receive oral tablets of eluxadoline (at a dose of 75 mg or 100 mg) or placebo twice daily. Randomization schedules were generated by a statistician who was aware of the patient assignments and who was not part of the operational statistical team (the members of which were unaware of the patient assignments), and were implemented centrally by an interactive voice-response system. The interactive voice-response system also served as the electronic patient diary and collected patient-reported daily symptoms of IBS with diarrhea, bowel functioning, and use of loperamide rescue treatment.

During the first 26 weeks of the IBS-3001 trial and the first 30 weeks of the IBS-3002 trial, the following assessments by patients were recorded daily: the score for the worst abdominal pain, the extent of discomfort and bloating (each scored on a scale of 0 to 10, with 0 indicating no symptoms and 10 indicating the worst imaginable symptoms), the stool consistency score, the number of bowel movements and whether they were associated with urgency or fecal incontinence, and the IBS-D global symptom score. In addition, adequate relief of IBS symptoms was assessed weekly.

In both studies, patient visits occurred at weeks 2, 4, 8, 12, 18, and 26. In addition, patient visits occurred at weeks 36, 44, and 52 in the IBS-3001 trial and at week 30 in the IBS-3002 trial. Quality of life was assessed with the use of the 34-item Irritable Bowel Syndrome Quality of Life (IBS-QOL) questionnaire (total scores range from 0 to 100, with higher scores indicating better quality of life) on day 1, at week 4, and at all subsequent visits through week 52.

Rescue medication was not allowed during the screening period; however, loperamide was allowed as needed during the double-blind period (at a dose of 2 mg every 6 hours, with no more than four doses over the course of 24 hours and no more than seven doses over the course of 48 hours).

STUDY OVERSIGHT

The trials were designed by the first author and the industry authors. Data collection was monitored by Pharmaceutical Product Development (PPD), a contract research organization, under the supervision of Furiex; data were analyzed by PPD and the industry authors. All the authors vouch for the completeness and veracity of the data and analyses and for the fidelity of this report to the study protocols, available at NEJM.org. The initial draft of the manuscript was written by the first author and was reviewed by all the authors. Editorial support was provided by a professional medical writer who was paid by the sponsor. All the authors contributed to the revision of the manuscript, made the decision to submit the manuscript for publication, and signed a confidentiality agreement with the sponsor.

The institutional review board or ethics committee at each participating site approved the protocols, and all patients provided written informed consent.

EFFICACY END POINTS

The primary efficacy end point was the proportion of patients who had a composite response (i.e., patients who recorded on ≥50% of the days a reduction of ≥30% from their average baseline score for their worst abdominal pain and, on the same days, a stool-consistency score of <5). If the patient did not have a bowel movement, an improvement of at least 30% in the score for the worst abdominal pain was sufficient for a response on that day. Responses were evaluated over the initial 12 weeks (the FDA end point) and 26 weeks (the European Medicines Agency [EMA] end point). A minimum of 60 diary-entry days from weeks 1 through 12 and 110 diary-entry days from weeks 1 through 26 were required for the patient to be considered to have had a response.

Secondary end points included the following: pain relief (reduction of ≥30% from baseline in the score for the worst abdominal pain on ≥50% of days), improvement in stool consistency (stool consistency score of <5, or the absence of a bowel movement if accompanied by an improvement of ≥30% in the score for the worst abdominal pain, on ≥50% of days), improvement in the global symptom score (a score of 0 or 1, or an improvement of ≥2 over the baseline score, on ≥50% of days), and adequate relief of IBS symptoms (a response of "yes" on ≥50% of the weeks to the following question: "Over the past week, have you had adequate relief of your IBS symptoms?"). In addition, the change from baseline in the IBS-QOL questionnaire score was assessed. As a secondary end point, the composite response was also evaluated over each 4-week interval.

SAFETY

Data on safety were collected for 26 weeks in the IBS-3002 trial and for 52 weeks in the IBS-3001 trial. Safety assessments included the assessment of adverse events and serious adverse events, laboratory testing, 12-lead electrocardiography, and physical examinations. In addition, at the end of study, the Subjective Opiate Withdrawal Scale[17] was used to assess potential symptoms of withdrawal. This scale includes 16 symptoms of withdrawal, each of which has a possible score of 0 to 4 for intensity (0 indicates no intensity, 1 minor intensity, 2 moderate intensity, 3 major intensity, and 4 extreme intensity). An adjudication committee was established to review events that were deemed to be suspicious for pancreatitis and cases of abdominal pain that were associated with elevated liver-enzyme levels.

STATISTICAL ANALYSIS

We estimated the sample size for each study assuming that 14% of the patients in the placebo group would meet the criteria for the primary end point and assuming a treatment effect of 10% for any eluxadoline group as compared with placebo. These calculations, which were based on interactions with global regulatory authorities, resulted in a sample of 375 patients per group in each study. We calculated that with this sample size, the study would have approximately 90% power to detect the 10% treatment effect, with the use of a two-sided Cochran–Mantel–Haenszel test, at a Bonferroni-adjusted alpha level of 0.025 to account for two active-treatment-group comparisons with placebo, thereby maintaining the family-wise alpha level. The treatment effect was assessed by means of pairwise Cochran–Mantel–Haenszel tests of eluxadoline versus placebo with respect to the primary composite response (weeks 1 through 12 and weeks 1 through 26). No other adjustments for multiplicity were made, since other analyses supported the primary analysis.

Patients were stratified according to the country in which they resided. Efficacy analyses involved the intention-to-treat population (i.e., all patients who underwent randomization). No imputation for missing data was performed, since the minimum compliance rules described above accounted for missing diary entries.

In addition, we performed a "worst case" analysis that required 50% positive-response days relative to the nominal days within the interval of interest in order for the patient to be considered to have had a response (an absolute number of ≥42 of 84 positive days from weeks 1 through 12 or ≥91 of 182 positive days from weeks 1 through 26, regardless of adherence to reporting in the electronic diary). This approach effectively imputed a nonresponse day for each day on which a diary entry was missing.

Efficacy analyses of pooled data from the two studies were prospectively planned, with emphasis on relevant subgroups, including subgroups defined according to age (<65 years vs. ≥65 years) and sex. Additional prospective pooled analyses included those that used alternative definitions of pain response (≥40% and ≥50% reduction in pain from baseline), analyses of the change from baseline in raw symptom scores, and analyses of the proportion of patients who had urgency-free days. We generally used statistical approaches (Cochran–Mantel–Haenszel tests) for pooled data analyses that were identical to those used for the individual studies. Potential treatment heterogeneities were evaluated by visual inspection of forest plots of odds ratios for each subgroup.

The safety population included patients who received at least one dose of either eluxadoline or placebo. Safety end points were summarized according to study group with the use of descriptive statistics and included data for all patients up to 52 weeks.

RESULTS

PATIENTS

A total of 2428 patients (1282 in the IBS-3001 trial and 1146 in the IBS-3002 trial) were enrolled. One patient in the IBS-3001 trial received a dose of eluxadoline but did not undergo randomization (Fig. S2 in the Supplementary Appendix). One patient in each trial underwent randomization twice (each tried to participate at more than one study site). Therefore, the intention-to-treat population consisted of 2425 patients (1280 in the IBS-3001 trial and 1145 in the IBS-3002 trial). Demographic and baseline characteristics were balanced across the groups and studies (Table 1).

EFFICACY

From weeks 1 through 12, the proportion of patients who were considered to have an FDA end-point response was significantly greater among those who received eluxadoline at a dose of 75 mg or 100 mg twice daily than among those who received placebo, both in the IBS-3001 trial (23.9% with the 75-mg dose and 25.1% with the 100-mg dose vs. 17.1% with placebo; P=0.01 for the comparison of 75 mg with placebo and P=0.004 for the comparison of 100 mg with placebo) and in the IBS-3002 trial (28.9% and 29.6%, respectively, vs. 16.2%; P<0.001 for the comparison of each dose of eluxadoline with placebo) (Fig. 1A). From weeks 1 through 26, the proportions of patients who were considered to have an EMA end-point response were 23.4% in the 75-mg group and 29.3% in the 100-mg group, versus 19.0% in the placebo group in the IBS-3001 trial (P=0.11 for 75-mg comparison and P<0.001 for the 100-mg comparison) and 30.4% and 32.7%, respectively, versus 20.2% in the IBS-3002 trial (P=0.001 for the 75-mg comparison and P<0.001 for the 100-mg comparison) (Fig. 1B). The treatment effect of eluxadoline over placebo was observed within the first week and was maintained throughout the 26-week assessment period (Fig. 2, and Table S1 in the Supplementary Appendix).

Similar results were seen in the worst-case analysis (Table 2). In addition, both doses of eluxadoline were significantly superior to placebo with respect to stool consistency, frequency, and urgency, although no significant reduction in episodes of incontinence was noted (Table 2, and Tables S2 and S3 in the Supplementary Appendix).

No significant improvement was seen in the mean scores for the worst abdominal pain or in the percentage of patients who reported an improvement of 30% or more in the score for the worst abdominal pain (Table 2). However, with the use of more stringent measures of reduction in these scores (i.e., ≥40% and ≥50%), significance was reached for eluxadoline at a dose of 100 mg in both study periods assessed (weeks 1 through 12 and weeks 1 through 26), as well as for eluxadoline at a dose of 75 mg from weeks 1 through 12 (Table S2 in the Supplementary Appendix). At week 12, the symptoms of abdominal bloating were significantly less severe among patients who received the 100-mg dose of eluxadoline than among those who received placebo (Table S3 in the Supplementary Appendix).

Both doses of eluxadoline were significantly superior to placebo with respect to the end points of adequate relief of IBS symptoms, scores for global symptoms, and scores on the IBS-QOL questionnaire (Table 2, and Table S3 in the Supplementary Appendix). Eluxadoline was significantly superior to placebo in all subpopulations explored (Fig. S3 in the Supplementary Appendix).

Table 1. Demographic and Baseline Characteristics of the Patients.*

Characteristic	IBS-3001 Trial			IBS-3002 Trial		
	Placebo (N=427)†	Eluxadoline, 75 mg (N=429)†	Eluxadoline, 100 mg (N=426)†	Placebo (N=382)†	Eluxadoline, 75 mg (N=381)†	Eluxadoline, 100 mg (N=383)†
Age — yr	45.8±14.1	44.5±13.2	44.4±13.9	47.1±13.8	45.0±13.2	45.7±13.3
Age ≥65 yr — no. of patients (%)	51 (11.9)	29 (6.8)	35 (8.2)	51 (13.4)	36 (9.4)	39 (10.2)
Sex — no. of patients (%)						
Female	277 (64.9)	278 (64.8)	283 (66.4)	250 (65.4)	261 (68.5)	257 (67.1)
Male	150 (35.1)	151 (35.2)	143 (33.6)	132 (34.6)	120 (31.5)	126 (32.9)
Race — no. of patients (%)‡						
Black	46 (10.8)	46 (10.7)	48 (11.3)	43 (11.3)	46 (12.1)	51 (13.3)
White	370 (86.7)	374 (87.2)	368 (86.4)	329 (86.1)	327 (85.8)	318 (83.0)
Body-mass index§	30.6±7.25	30.7±7.42	31.2±7.86	29.8±6.9	30.8±8.2	30.5±7.7
History of cholecystectomy — no. of patients (%)	89 (20.8)	85 (19.8)	98 (23.0)	69 (18.1)	81 (21.3)	74 (19.3)
Mean daily scores						
Abdominal pain¶	6.2±1.6	6.1±1.5	6.2±1.5	6.0±1.5	6.0±1.5	6.0±1.5
Stool consistency‖	6.3±0.4	6.3±0.4	6.3±0.4	6.2±0.4	6.2±0.4	6.2±0.4
Abdominal bloating score¶	6.1±2.0	5.9±2.0	5.8±2.1	5.7±2.1	5.7±2.0	5.6±2.0
IBS-D global symptom score**	2.9±0.5	2.8±0.5	2.9±0.5	2.8±0.5	2.8±0.5	2.8±0.5
IBS-QOL questionnaire score††	44.1±23.0	46.2±23.3	45.9±22.6	46.7±23.2	50.6±23.1	48.7±23.4
Episodes of urgency — no.‡‡	3.7±2.7	3.5±2.2	3.5±2.1	3.4±2.0	3.4±2.2	3.6±4.1
Average daily bowel movements — no.‡‡	5.0±2.7	4.9±2.7	5.0±3.0	4.7±2.2	4.7±2.3	4.9±4.2

* Plus–minus values are means ±SD. There were no significant differences between the three groups. IBS denotes irritable bowel syndrome, and QOL quality of life.
† Eluxadoline and placebo were administered twice a day.
‡ Race was self-reported.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ The score for the worst abdominal pain and the abdominal bloating score were each recorded on a scale of 0 to 10, with 0 indicating no symptoms and 10 the worst imaginable symptoms.
‖ Stool consistency was assessed with the use of the Bristol Stool Form Scale, which ranges from 1 to 7, with 1 indicating hard stool and 7 indicating watery diarrhea.
** The IBS-D global symptom score was based on a scale of 0 to 4, with 0 indicating no symptoms and 4 very severe symptoms.
†† The IBS-QOL questionnaire consists of 34 items, each with a five-point response scale, with 1 indicating better quality of life and 5 worse quality of life.
‡‡ Frequency and urgency were recorded as the number of bowel movements and the number of episodes of urgency over the previous 24 hours.

SAFETY

Safety data were obtained from all patients up to 26 weeks (IBS-3002 trial) and through 52 weeks (IBS-3001 trial). There were no treatment-related trends in mean levels of serum chemical values or hematologic values over time. Although isolated renal and metabolic events were reported, there was no pattern across the study groups.

The most common adverse events were nausea, constipation, and abdominal pain (Table 3). Discontinuation of eluxadoline or placebo owing to adverse events was infrequent. The rate of discontinuation due to constipation was 1.1% among patients who received eluxadoline at a dose of 75 mg, 1.7% among patients who received eluxadoline at a dose of 100 mg, and 0.2% among patients who received placebo. The rate of discontinuation due to nausea was 0.6% and 0% among patients who received 75-mg and 100-mg doses of eluxadoline, respectively, and 0.5% among patients who received placebo.

No deaths were reported during the study.

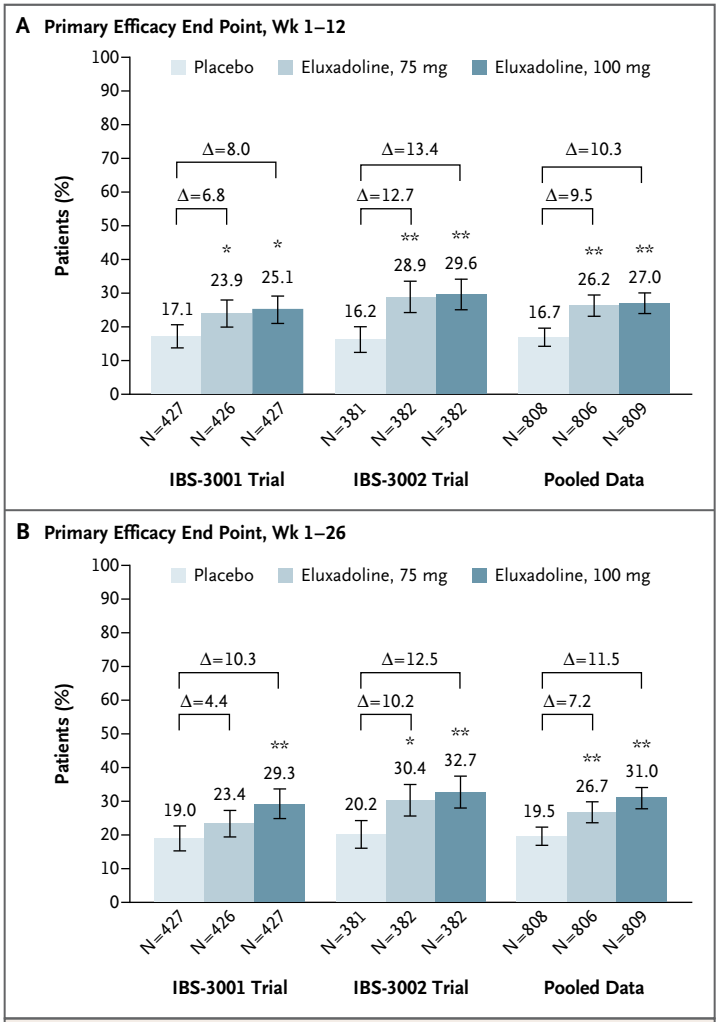

Figure 1. Primary Efficacy End Point in the Eluxadoline and Placebo Groups in Each Trial and in the Pooled Trials.

The primary efficacy end point was defined as the proportion of patients who recorded a reduction of 30% or more from baseline in the daily average score for their worst abdominal pain for at least 50% of days assessed and, on the same days, a daily stool-consistency score of less than 5 (on a scale of 1 to 7, with 1 indicating hard stool and 7 indicating watery diarrhea), for weeks 1 through 12 (Panel A) and for weeks 1 through 26 (Panel B). The single asterisk denotes $P<0.05$ vs. placebo, and the double asterisk $P<0.001$ vs. placebo.

A single case of self-limited ischemic colitis occurred in a 72-year-old woman who received 100 mg of eluxadoline; she had a history of cirrhosis and was receiving aspirin. Serious adverse events occurred in 4.2% of the patients who received eluxadoline at a dose of 75 mg, 4.8% of the patients who received eluxadoline at a dose of 100 mg, and 3.0% of the patients who received placebo. Two patients in the 100-mg eluxadoline group had respiratory failure; one had numerous predisposing risk factors, whereas the other had an exacerbation of asthma that resulted in a stress cardiomyopathy (Table S4 in the Supplementary Appendix).

Five patients (two in the 75-mg eluxadoline group and three in the 100-mg eluxadoline group) had serious adverse events that were determined by the adjudication committee to be pancreatitis. Eight patients (one who received eluxadoline at a dose of 75 mg and seven who received eluxadoline at a dose of 100 mg) had acute abdominal pain associated with abrupt increases in liver-enzyme levels; in one of the eight patients, this adverse event was serious. One of the five cases of pancreatitis (in the 100-mg group) and all eight cases of abdominal pain with elevation of hepatic enzyme levels were determined by the adjudication committee to be consistent with spasm of the sphincter of Oddi. This determination was made after the committee's positive response to the question "Is the event consistent with an acute reversible pancreatic or biliary duct obstruction?" All nine of these cases were associated with the absence of a gallbladder, and seven occurred within 2 weeks after the initiation of treatment. Of the remaining four events of pancreatitis, one was associated with biliary sludge and three were associated with excessive alcohol consumption (additional information was collected retrospectively).

Adverse reactions of euphoria were not reported among any patients who received eluxadoline at a dose of 75 mg; these reactions were reported in 0.2% of the patients (2 of 859 patients) who received eluxadoline at a dose of 100 mg. Adverse reactions of feeling drunk were reported in 0.1% of the patients who received 75 mg of eluxadoline (1 of 807 patients) and in 0.1% of patients who received 100 mg of eluxadoline (1 of 859 patients). Neither of these reactions were reported in the placebo group.

Neither symptoms recorded daily during the single-blind placebo withdrawal period nor the adverse-event profile during the follow-up periods suggested any worsening of symptoms of IBS with diarrhea or symptoms of withdrawal after the end of treatment (Tables S5 and S6, and Fig. S4 in the Supplementary Appendix). Median scores on the Subjective Opiate Withdrawal Scale, on which scores range from 0 to 64, with higher scores indicating more intense symptoms of

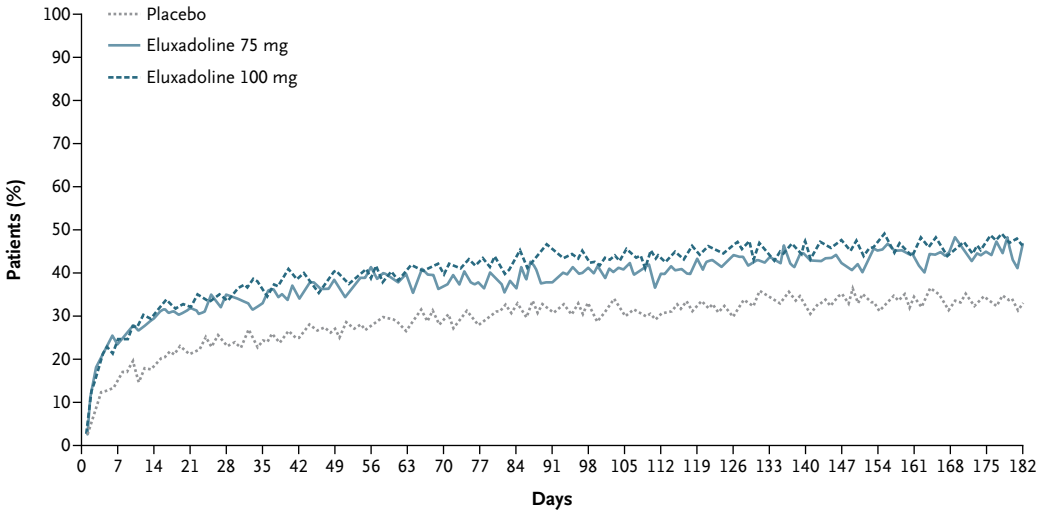

Figure 2. Percentage of Patients Who Met the Daily Composite Response Criteria over Time.
Data are pooled from the two phase 3 studies.

withdrawal, were nearly identical in the eluxadoline and placebo groups. The median scores were 2 (range, 0 to 54) among the patients who received eluxadoline at a dose of 75 mg, 3 (range, 0 to 56) among the patients who received eluxadoline at a dose of 100 mg, and 3 (range, 0 to 56) among the patients who received placebo.

DISCUSSION

In these studies involving patients with IBS and diarrhea, eluxadoline was effective in simultaneously relieving the symptoms of abdominal pain and diarrhea. Our primary outcome measure required simultaneous improvement in the daily scores for the worst abdominal pain and stool consistency on the same day for at least 50% of the days assessed; this end point is currently one of those recommended by the regulatory agencies in the United States and Europe to show treatment effect in trials involving patients with IBS and diarrhea. More patients who received eluxadoline than who received placebo reported significant improvement in the primary outcome measure over both intervals assessed (absolute differences for the two doses across the two studies ranged from 7 to 13 percentage points for weeks 1 through 12, and from 4 to 13 percentage points for weeks 1 through 26; the difference for the 75-mg dosage was not statistically significant for weeks 1 through 26 in one study).

Patients who received eluxadoline reported a decrease in stool frequency and in urgency, which are two of the most bothersome symptoms of IBS with diarrhea. Eluxadoline was also significantly superior to placebo with respect to global assessments (on measures of adequate relief of IBS symptoms, global symptoms, and quality of life), particularly at the 100-mg twice-daily dose, with treatment effects on adequate relief of IBS symptoms that were similar to those reported with alosetron and rifaximin.[5,18] The use of eluxadoline did not result in significantly higher rates of the prespecified secondary outcome of 30% improvement in the average score for the worst abdominal pain than the rates with placebo. Significant differences were seen when higher thresholds of improvement in this score (i.e., ≥40% and ≥50%) were assessed (Table S2 in the Supplementary Appendix). Studies of loperamide have shown a decrease in diarrhea but minimal effect on abdominal pain.[19-21]

The most common adverse events in the patients who received eluxadoline at a dose of 100 mg were constipation (in 8.6% of the patients) and nausea (in 7.5%). Rates of discontinuation due to adverse events were infrequent (among 1.1%, 1.7%, and 0.2% of patients because of constipation and among 0.6%, 0%, and

Table 2. Secondary Efficacy End Points (Weeks 1–12).

End Point	IBS-3001 Trial*					IBS-3002 Trial*				
	Placebo (N=427)	Eluxadoline, 75 mg (N=427)	P Value	Eluxadoline, 100 mg (N=426)	P Value	Placebo (N=382)	Eluxadoline, 75 mg (N=381)	P Value	Eluxadoline, 100 mg (N=382)	P Value
	no. of patients with response (%)			*no. of patients with response (%)*		*no. of patients with response (%)*			*no. of patients with response (%)*	
Worst-case analysis	71 (16.6)	100 (23.4)	0.01	103 (24.2)	0.006	53 (13.9)	108 (28.3)	<0.001	108 (28.3)	<0.001
Abdominal pain†	169 (39.6)	181 (42.4)	0.40	184 (43.2)	0.28	173 (45.3)	183 (48.0)	0.45	195 (51.0)	0.11
Stool consistency‡	94 (22.0)	128 (30.0)	0.008	146 (34.3)	<0.001	80 (20.9)	141 (37.0)	<0.001	136 (35.6)	<0.001
IBS-D global symptoms§	123 (28.8)	150 (35.1)	0.05	148 (34.7)	0.06	113 (29.6)	166 (43.6)	<0.001	162 (42.4)	<0.001
Adequate relief of IBS symptoms¶	187 (43.8)	226 (52.9)	0.008	231 (54.2)	0.002	188 (49.2)	229 (60.1)	0.003	223 (58.4)	0.01

* Eluxadoline and placebo were administered twice a day.

† A patient who had a response was defined as a patient who met the daily pain response criterion (worst abdominal pain score in the past 24 hours improved by ≥30%, as compared with baseline pain) on 50% of days or more on which this outcome was recorded in an electronic diary during the interval and who had a minimum of 60 days of diary data from weeks 1 through 12.

‡ A patient who had a response was defined as a patient who met the daily stool consistency response criterion (Bristol Stool Form Scale score <5, or a diary entry reporting the absence of a bowel movement if accompanied by a ≥30% improvement in worst abdominal pain score as compared with baseline) on 50% of days or more on which this outcome was recorded in an electronic diary during the interval and who had a minimum of 60 days of diary data from weeks 1 through 12.

§ The IBS-D global symptom score is based on a scale of 0 to 4, with 0 indicating no symptoms and 4 very severe symptoms. A patient who had a response was defined as a patient who met the daily IBS-diarrhea global symptom score criterion (a global symptom score of 0 or 1, or a daily score improved by ≥2.0 as compared with the baseline average) on 50% of days or more during the interval and who had a minimum of 60 days of diary data from weeks 1 through 12.

¶ A patient who met this end point had a weekly response of "yes" when asked whether he or she had adequate relief of symptoms of IBS with diarrhea for 50% or more of the total weeks during the interval and had a minimum of 6 weeks of data for the 12-week interval.

Table 3. Common Adverse Events.*

Event	Placebo (N=808)†	Eluxadoline		
		75 mg (N=807)†	100 mg (N=859)†	Combined Groups (N=1666)†
		no. of patients (%)		
Adverse events				
All adverse events	450 (55.7)	486 (60.2)	500 (58.2)	986 (59.2)
Serious adverse events	24 (3.0)	34 (4.2)	41 (4.8)	75 (4.5)
Cardiac events	8 (1.0)	12 (1.5)	17 (2.0)	29 (1.7)
Pancreatitis	0	2 (0.2)	3 (0.3)	5 (0.3)
Spasm of the sphincter of Oddi	0	1 (0.1)	7 (0.8)	8 (0.5)
Most common adverse events‡				
Constipation§	20 (2.5)	60 (7.4)	74 (8.6)	134 (8.0)
Nausea	41 (5.1)	65 (8.1)	64 (7.5)	129 (7.7)
Abdominal pain¶	33 (4.1)	47 (5.8)	62 (7.2)	109 (6.5)
Vomiting	11 (1.4)	32 (4.0)	36 (4.2)	68 (4.1)
Abdominal distention	13 (1.6)	21 (2.6)	22 (2.6)	43 (2.6)
Gastroenteritis‖	27 (3.3)	36 (4.5)	19 (2.2)	55 (3.3)
Flatulence	13 (1.6)	21 (2.6)	27 (3.1)	48 (2.9)
Upper respiratory tract infection	32 (4.0)	27 (3.3)	47 (5.5)	74 (4.4)
Bronchitis	18 (2.2)	26 (3.2)	27 (3.1)	53 (3.2)
Sinusitis	26 (3.2)	27 (3.3)	24 (2.8)	51 (3.1)
Nasopharyngitis	27 (3.3)	33 (4.1)	23 (2.7)	56 (3.4)
Dizziness	17 (2.1)	21 (2.6)	28 (3.3)	49 (2.9)
Anxiety	14 (1.7)	10 (1.2)	19 (2.2)	29 (1.7)
Increased level of alanine aminotransferase	12 (1.5)	17 (2.1)	26 (3.0)**	43 (2.6)

* Values are pooled data from the IBS-3001 trial (52 weeks of double-blind safety data) and the IBS-3002 trial (26 weeks of double-blind safety data). The respective durations (person-years) of exposure were as follows: placebo group, 433.6 person-years; 75-mg eluxadoline group, 417.4 person-years; 100-mg eluxadoline group, 429.5 person-years; and the combined eluxadoline groups, 846.9 person-years.

† Eluxadoline and placebo were administered twice a day for 52 weeks in the IBS-3001 trial and for 26 weeks in the IBS-3002 trial.

‡ The most common adverse events listed were reported in 2.0% or more of the patients in any of the study groups.

§ All constipation events were nonserious. A total of 1.4% of patients who received eluxadoline and 0.2% who received placebo discontinued their use because of nonserious constipation.

¶ The term "abdominal pain" includes the conditions coded as abdominal pain, upper abdominal pain, and lower abdominal pain.

‖ The term "gastroenteritis" includes the conditions coded as gastroenteritis and viral gastroenteritis.

** Seven of the 26 cases of increased levels of alanine aminotransferase occurred in patients who were determined by the adjudication committee to have spasm of the sphincter of Oddi.

0.5% of patients because of nausea in the 75-mg eluxadoline, 100-mg eluxadoline, and placebo groups, respectively). In trials of alosetron, the rates of discontinuation due to adverse events were 10 to 15% among patients who received alosetron and 7 to 9% among patients who received placebo.[22,23]

Five cases of pancreatitis (0.3%) and 8 cases of abdominal pain with elevated levels of hepatic enzymes (0.5%) occurred in this study. Nine of these 13 cases were determined by the adjudication committee to be associated with spasm of the sphincter of Oddi. All cases of pancreatitis did not involve organ failure or local or systemic

complications, occurred in patients with either biliary disorders (spasm of the sphincter of Oddi and biliary sludge) or alcohol use (3 of 5 cases), and resolved within the first week after the onset of pancreatitis.[24] The presence of only mild cases does not preclude the risk of severe cases in the future, nor do these associations preclude other at-risk populations. Data are lacking from studies to assess whether the risk of pancreatitis can be reduced if treatment is restricted to patients with gallbladders or to those who abstain from excessive alcohol use. Identifying patients with IBS with diarrhea who are at risk for acute pancreatitis because of the absence of a gallbladder or excessive alcohol consumption is important before initiating therapy with eluxadoline. Any benefit will need to be considered in the context of side effects and risks.

Alcohol has been shown to alter pancreatic ductal and periductal anatomy,[25-27] as well as to contribute to increases in pressure at the sphincter of Oddi,[28,29] which may have exacerbated the known association of pancreatitis[30-35] and spasm of the sphincter of Oddi with μ-opioid receptor agonists.[36-43] Spasm of the sphincter of Oddi occurred exclusively in patients who did not have a gallbladder; there were no cases of spasm of the sphincter of Oddi among the 1318 patients with a gallbladder who received eluxadoline.

In summary, in two phase 3 trials involving women and men with IBS with diarrhea, treatment with eluxadoline, a poorly absorbed,[12] peripherally active, mixed κ- and μ-opioid receptor agonist and δ-opioid receptor antagonist, resulted in a decrease in symptoms of IBS with diarrhea. Pancreatitis developed in 5 of 1666 patients (0.3%), and abdominal pain with elevated hepatic-enzyme levels developed in 8 of 1666 patients (0.5%). Future studies should be aimed at identifying subpopulations of patients with IBS with diarrhea who may best benefit from eluxadoline.

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