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