Spotlight on eluxadoline for the treatment of patients with irritable bowel syndrome with diarrhea

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Background: Irritable bowel syndrome with diarrhea (IBS-D) has limited options for treatment currently, including mainly anti-motility medications, antispasmodics, and antidepressants. This review discusses the properties of a new drug, eluxadoline, a gut-targeting mu- and kappa-opioid receptor agonist and a delta-opioid receptor antagonist, and its efficacy and safety in patients with IBS-D.

Materials and methods: A systematic review of the literature was undertaken to identify studies that had investigated eluxadoline as a treatment in IBS-D. A narrative review of other information is provided with respect to pharmacological and chemical properties. Where suitable, meta-analysis was performed with a random-effects model to produce a pooled estimate.

Results: Eluxadoline showed efficacy improving stool consistency (standardized mean difference [SMD]: -0.29 at 12 weeks, $p = 0.0004$; -0.46 at 26 weeks, $p = 0.0001$), global symptoms (SMD: -0.15 at 12 weeks, $p = 0.006$; -0.14 at 26 weeks, $p = 0.02$), quality of life (SMD: 0.21 at 12 weeks, $p < 0.0001$; 0.16 at 26 weeks, $p = 0.007$), pain (SMD: -0.17 at 12 weeks, $p = 0.001$; -0.16 at 26 weeks, $p = 0.01$), and adequate relief (odds ratio [OR]: 1.99 at 12 weeks, $p < 0.00001$; 1.78 at 26 weeks, $p < 0.0001$). It also improved IBS severity and other abdominal symptoms such as bloating, discomfort, and risk of urgency and fecal incontinence. Its main side effects included constipation (OR: 3.49, $p < 0.00001$), vomiting (OR: 3.42, $p = 0.0002$), abdominal pain (OR: 1.78, $p = 0.007$), and nausea (OR: 1.42, $p = 0.07$). The overall quality of trials was satisfactory with the meta-analyses providing largely homogeneous outcomes.

Conclusion: Eluxadoline's place in clinical practice might prove useful since the pharmacological options of IBS-D are limited and eluxadoline showed a positive effect in treating the symptoms of IBS-D.

Keywords: eluxadoline, irritable bowel syndrome, diarrhea, stool consistency, pain

Plain language summary

The current review summarizes the benefits of a new drug, eluxadoline, on the symptoms of irritable bowel syndrome with diarrhea in adults. Eluxadoline works on special receptors of the gut slowing the gut transit time. All studies comparing eluxadoline with placebo were searched in the scientific literature. Mathematical analysis of the available studies showed that patients who received eluxadoline had better stool consistency, quality of life, pain, and adequate relief. Patients' irritable bowel syndrome symptoms were less and also less serious. Its main disadvantages were difficulty passing stools, throwing up, feeling sick, and tummy pain. Care should be taken and specialist advice should be sought when using eluxadoline, because it can interact with certain medications and should not be used on patients at risk of pancreatitis.

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Introduction

Recurrent abdominal pain associated with defecation or a change in bowel habits is considered a functional bowel disorder termed irritable bowel syndrome (IBS).[1,2] It can present predominantly with diarrhea, constipation, and a mixed or unspecified clinical picture. IBS with diarrhea (IBS-D) is diagnosed when more than 25% of bowel movements present as Bristol stool form types 6 or 7 and less than 25% of bowel movements present as Bristol stool form types 1 or 2 (clinically termed diarrhea).[3] Symptoms should be present during the last 3 months having started at least 6 months before diagnosis. The global prevalence of IBS is around 11%,[4] with significant morbidity since up to one-third of people who experience IBS symptoms will consult a physician.[5–7] Among IBS diagnoses, IBS-D is the most frequent diagnosis (around 40%).[4,8,9]

IBS is considered a multifactorial disorder with an unknown yet pathophysiological mechanism.[10,11] Significant attention has been given to variations in visceral hypersensitivity and gastrointestinal motility, with inflammation, alterations in fecal flora, bacterial overgrowth, food sensitivities, genetic predisposition, and psychosocial characteristics having been investigated as contributory factors.[12,13] Under the biopsychosocial conceptual model for IBS, it is predominantly associated with impaired quality of life (QoL) and increased health care use.[14,15]

Treatment options for IBS-D are essentially few, and national and international bodies recommend as first-step dietary, lifestyle modifications, and psychological interventions along with pharmacological agents, with variable success.[16] Each treatment approach tackles a different aspect of the pathogenetic mechanism of IBS. Pharmacologically, antidiarrheals (e.g., loperamide), antispasmodics (e.g., mebeverine and hyoscine), tricyclic antidepressants (e.g., amitriptyline) and selective serotonin reuptake inhibitors (e.g., citalopram) have been commonly used. Neomycin, rifaximin, probiotics, alosetron, ramosetron, and ondansetron have shown some effect in certain studies in IBS-D.[17–19]

A new drug in the treatment for patients with IBS-D is eluxadoline (Viberzi™, Truberzi™; Allergan Ltd, Dublin, Ireland). It was approved in May 2015 by the US Food and Drug Administration (FDA) and September 2016 by the European Medicines Agency (EMA) as a new agent for IBS-D[20] and has been recommended as a possible third-line option for IBS-D by the National Institute for Health and Care Excellence (NICE), UK.[21] In the current paper, we review its efficacy and safety with methods of systematic review and meta-analysis. First, we give a brief overview of eluxadoline's market history, biochemistry, and pharmacology.

Eluxadoline and the gut opioid system

The endogenous opioid system is composed of cell surface receptors (mu-opioid receptor, delta-opioid receptor, kappa-opioid receptor) and their endogenous ligands (beta-endorphin, enkephalins, dynorphins).[22] Opioid receptors are found within the enteric nervous system in the myenteric and submucosal plexuses, as well as muscular and immune cells in the stomach and intestine, in high concentrations influencing secretory and motor function after the release of the endogenous opioid peptides.[23] In particular, mu-opioid receptor agonists promote delay in gastric emptying and small and large intestine transit; increase pyloric tone; induce phasic pressure activity in the pylorus, duodenum, and jejunum; alter the migrating myoelectric complex; and cause an elevation in the resting anal sphincter pressure.[19,24,25] Hence, mu-opioid receptor agonists (e.g., morphine) promote constipation. Research has shown that delta-opioid receptor antagonists counteract this resulting constipation and increase the analgesia from mu-opioid receptor agonism.[22,26,27]

IBS-D is commonly characterized by pain and diarrhea, and eluxadoline was developed with a view to address both these symptoms.[20,28] Eluxadoline is an amino acid amide with a molecular weight of 569.65 g/mol and a molecular formula of $C_{32}H_{35}N_5O_5$; 5-[[[(2S)-2-amino-3-[4-(aminocarbonyl)-2,6-dimethylphenyl]-1-oxopropyl][(1S)-1-(4-phenyl-1H-imidazol-2yl)ethyl]amino]methyl]-2-methoxybenzoic acid (Figure 1).

Eluxadoline is a mu- and kappa-opioid receptor agonist and a delta-opioid receptor antagonist which functions in the gut.[19,29–31] It has poor oral bioavailability and is used for its local effects at opiate receptors in the gastrointestinal tract.[20] Eluxadoline is a schedule IV drug in the US, subject to control under the Federal Controlled Substances Act of 1970, in the same class with tramadol and benzodiazepines.[20,28]

The zwitterionic nature of eluxadoline leads it to be negative across the gastrointestinal pH range leading to poor
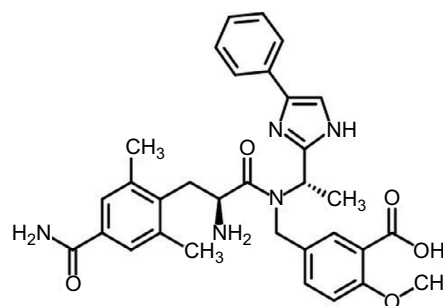

Figure 1 Chemical structure of eluxadoline.

oral absorption (1.02%). Eluxadoline plasma concentrations were very low post oral administration of 100 mg tablets (C_{max} ~ 2–4 ng/mL, median time to C_{max} was 1.5–2 hours, irrespective of whether the patient was fed or fasted),[20,28] and when given with a high-fat meal maximum plasma concentration decreased by 50%. Eluxadoline is mostly excreted in feces (82%), and less than 1% is excreted in urine. The metabolism of eluxadoline involves possibly limited glucuronidation forming an acyl glucuronide metabolite that is then excreted into urine with mean plasma elimination half-life ranging from 3.7 to 6 hours.[32]

Ex vivo and in vivo studies demonstrated that eluxadoline in combination with a delta-opioid receptor antagonist reduced intestinal contractility in isolated guinea pig ileum, decreased neurogenically evoked secretion in mouse small intestine and colon compared with loperamide, and normalized gut transit at 10- to 20-fold the minimum effective dose.[24,25] Other data suggest that delta-opioid receptors play a role in the mechanism of action of eluxadoline possibly mediated through the mu-opioid and delta-opioid heteromer at the level of the myenteric plexus and the longitudinal smooth muscle.[33] Regarding toxicity, no sign of central nervous system effect was shown with no behavioral changes or signs of withdrawal in monkeys or rats.[34] With regard to studies in human beings, as part of the drug development program, the abuse potential of eluxadoline compared with placebo and oxycodone has been tested in two studies.[34] These demonstrated that supratherapeutic doses of oral or intranasal eluxadoline did not result in similar effects as from oxycodone, which was used as a mu-agonist positive control, although eluxadoline was associated with euphoric mood in therapeutic doses.

In vitro studies did not indicate interaction of eluxadoline with cytochrome P450 hepatic enzyme systems, and apart from slow glucuronide metabolite formation found in urine after a 1000 mg dose, eluxadoline does not seem to be metabolized in the liver.[32,35] The potential for drug–drug interactions with eluxadoline is low.[28] Metabolic pathways of eluxadoline have not been fully elucidated, and the potential exists for concomitant use of potent CYP inhibitors (e.g., bupropion, ciprofloxacin, clarithromycin, fluconazole, gemfibrozil, and paroxetine) to increase exposure to eluxadoline. As a precautionary measure, patients should be monitored for impairment of mental or physical abilities required for the performance of potentially hazardous tasks (e.g., driving a car and operating machinery) and for other eluxadoline-related adverse effects.[28]

Eluxadoline is a substrate and inhibitor of the hepatic uptake transporter organic anion transport protein 1B1 (OATP1B1),[32] and its use is contraindicated in patients receiving potent OATP1B1 inhibitors (e.g., ciclosporin), where a lower dose of eluxadoline is recommended (75 mg twice per day). Although no dosage adjustment is needed when OATP1B1 substrates (e.g., rosuvastatin) are coadministered with eluxadoline, caution should be exercised in patients receiving high doses of OATP1B1 substrates. The concomitant use of other medications that can cause constipation, such as anticholinergics or 5-hydroxytryptamine $(HT)_3$ antagonists, is discouraged because of eluxadoline's potential additive effect.[28]

Eluxadoline is recommended to be taken at 100 mg twice daily with food or 75 mg twice daily with food if the patient has had a cholecystectomy, is being coadministered OATP1B1 inhibitors, or has mild or moderate hepatic impairment or cannot tolerate the higher dose.[26,28,36] Contraindications for treatment are history of constipation, gastrointestinal obstruction, biliary duct obstruction, sphincter of Oddi dysfunction, alcohol excess, a history of pancreatitis or pancreatic disease, and severe hepatic impairment.[26,28,36]

Clinical effectiveness
Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for systematic reviews and meta-analyses was followed.[37] PubMed/Medline, Scopus, EMBASE, and Cochrane library with no year limits were searched for studies. All randomized controlled trials involving eluxadoline in the treatment of IBS were considered. Exclusion criteria were non-randomized studies, pharmacological studies, and other types of articles (e.g., reviews, letters, and notes). The overall number of studies was 66 which eventually narrowed down to three randomized controlled trials: IBS-2001 (Phase II study),[38] IBS-3001, and IBS-3002 (two Phase III studies; Figure 2).[1,39–41] The studies are described in Table 1. The quality of studies (risk of bias) was assessed with Cochrane Collaboration's tool.[42] RevMan software package (Review Manager, Version 5.2; The Cochrane Collaboration, Oxford, UK) was employed for statistical analyses. Dichotomous and continuous data between two groups were estimated with an odds ratio (OR) and the standardized mean difference (SMD) with two-tailed 95% CI, respectively. SMD values of 0.2, 0.5, and 0.8 were defined as small, moderate, and large effect size, respectively.[43] Random-effects meta-analysis was used throughout the current review
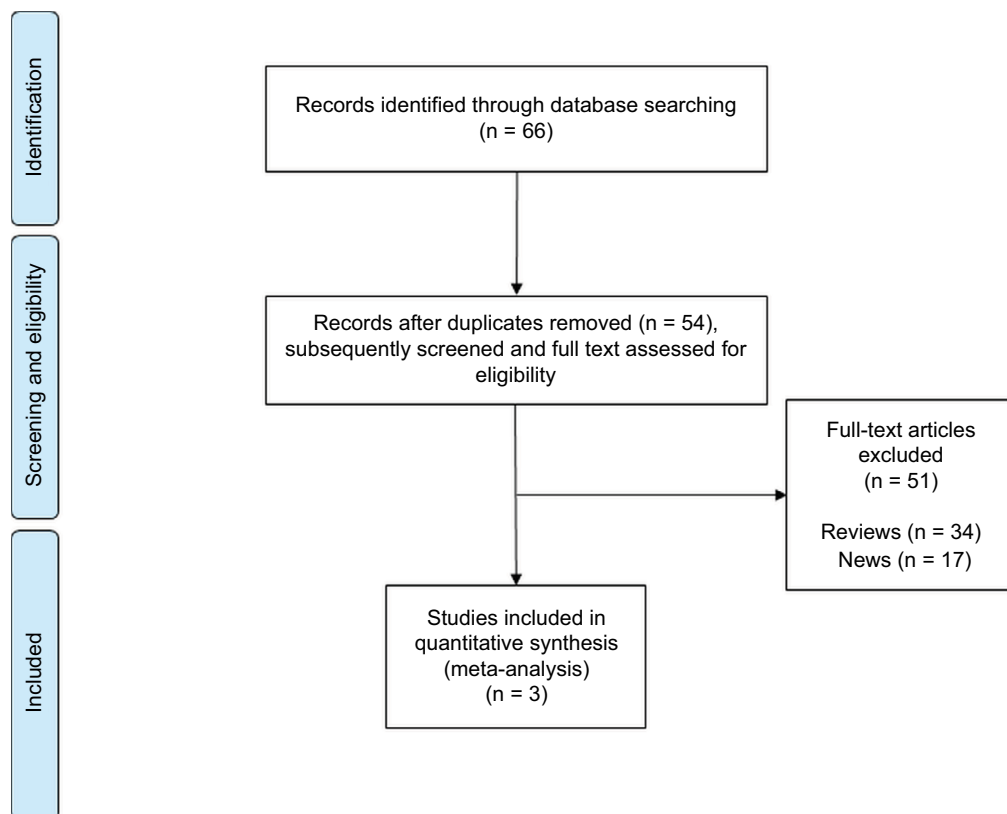
Figure 2 Flowchart of studies.

to account for heterogeneity between studies. The statistic I^2 was used to quantify the degree of heterogeneity with a score of 25%, 50%, and 75% representing low, moderate, and high levels of inconsistency, respectively. Statistical significance was regarded as $p < 0.05$ throughout the study.[44]

Clinical effectiveness analysis
Eluxadoline trials: IBS-2001, IBS-3001, and IBS-3002
The efficacy and safety of eluxadoline was investigated in one Phase II (IBS-2001)[38] and two Phase III (IBS-3001 and IBS-3002)[1,39–41] randomized controlled trials. The overall number of subjects was 3,235 adults with IBS-D (as defined by Rome III criteria)[45] participating in large, international, multicenter, placebo-controlled studies. The clinical trials were designed to meet a robust composite end point, defined by the FDA and Committee for Medicinal Products for Human Use (CHMP). Overall, eluxadoline provides an effective and tolerable treatment option in this condition albeit being considered to present a mild-to-moderate effect (as given in the "Methods" section). The outcome measures investigated included: stool consistency, abdominal pain, abdominal bloating, frequency of bowel movements, urgency of bowel movements, severity of symptoms, duration of response to treatment, adverse effects of treatment, and health-related QoL.

IBS-2001 was the first randomized, double-blind, controlled Phase II clinical trial in which 807 patients were assigned to groups who received oral placebo or eluxadoline 5, 25, 100, or 200 mg twice daily for 12 weeks.[38] The primary end point was the number of composite clinical responses at week 4, defined by having completed 5-out-of-7-days diary entries, and had an improvement by ≥30% and at least 2 points in average daily pain scores as well as a stool consistency score of 3 or 4 on the Bristol Stool Scale for at least 66% of daily diary entries during that week.[35] At week 4, more patients receiving treatment with 25 and 200 mg eluxadoline met the primary end point of clinical response when compared with placebo (12% vs 13.8% vs 5.7%, respectively; $p < 0.05$). At week 12, this effect was sustained with 100 mg eluxadoline, with more clinical responders compared with placebo (20.2% vs 11.3%, respectively; $p < 0.05$). At week 4, there was a statistically significant increase in the number of stool consistency responders in those taking 25 and 200 mg eluxadoline when compared with placebo (16.8% vs 18.1% vs 8.2%, respectively; $p < 0.05$).

Although 200 mg eluxadoline had achieved a significant decrease in IBS Global Symptom Scores compared with placebo by week 4, which was sustained at weeks 8 and 12

Table 1 Randomized controlled trials of eluxadoline for IBS-D

Design	Number of participants	Primary and secondary end points	Dose and duration	Inclusion criteria
IBS-2001: randomized, double-blind, placebo-controlled, multicenter study[38]	• Total: 807 • Eluxadoline: 635 • Placebo: 172	• Primary outcome: number of composite clinical responses at week 4. A patient was defined as a clinical responder if they completed 5-out-of-7-days of diary entries and met both of the following criteria: an improvement by ≥30% and at least 2 points in average daily pain scores as compared with baseline and achieved a Bristol Stool Scale score of 3 or 4 on >66% of reported days in the past week • Secondary outcomes: composite clinical responders after 12 weeks; abdominal pain responders, stool consistency responders, adequate relief responders, frequency of bowel movements; urgency episodes, incontinence episodes, changes in IBS global symptoms, QoL, and severity scores	Eluxadoline: 5 or 25 or 100 or 200 mg twice per day by mouth vs placebo twice per day for 12 weeks	• Age: 18–65 years old • IBS-D defined by Rome III criteria • Average of daily pain scores of ≥3.0 on a 0–10-point scale • Weekly mean Bristol Stool Scale score equal to or over 5.5 • Colonoscopy within the past 5 years for any alarm feature • Stable diet and no use of rescue medication within 14 days of randomization • Female patients: postmenopausal or surgically sterile or abstinent or receiving contraception, if sexually active
IBS-3001, IBS-3002: prospective, double-blind placebo-controlled, multicenter studies[1,39–41]	• Total: 2428 • Eluxadoline: 1616 • Placebo: 809	• Primary outcome: number of composite clinical responders over 26 weeks. Clinical responder: if they met the daily response criteria for at least half of the days with diary entries. On a given day, both of the below should be satisfied: daily pain response (worst abdominal pain scores in the past 24 hours improved by ≥30% compared with baseline) and daily stool consistency response (Bristol Stool Scale score < 5 or the absence of a bowel movement if accompanied by ≥30% improvement in worst abdominal pain compared with baseline pain). • Secondary outcomes: abdominal pain responders defined as those patients who met the daily pain response criteria; stool consistency responders, adequate relief responders, frequency of bowel movements; urgency episodes, incontinence episodes, changes in IBS global symptoms, and QoL	Eluxadoline: 75 or 100 mg twice per day by mouth vs placebo twice per day for 26 weeks	• Age: 18–80 years old • IBS-D defined by Rome III criteria • Average of worst abdominal pain scores of ≥3.0 on a 0–10-point scale • Average mean Bristol Stool Scale of ≥5.5 and at least 5 days with a Bristol Stool Consistency Scale score ≥5 on a 1–7-point scale • Average daily IBS-D Global Symptom Score of ≥2.0 on a 0–4-point scale • Stable diet and no use of rescue medication within 14 days of randomization • Female patients: postmenopausal or surgically sterile or abstinent or receiving contraception, if sexually active

Abbreviations: IBS-D, irritable bowel syndrome with diarrhea; QoL, quality of life.

(-0.26, -0.30, -0.34, respectively; $p < 0.001$), 100 mg eluxadoline achieved a similar effect in weeks 8 and 12 (-0.19, -0.26, respectively; $p < 0.05$). Similarly, mean differences in IBS Symptom Severity Scores from placebo were statistically significant for the 100 mg eluxadoline group at the end of weeks 4, 8, and 12 (-16.69, -33.55, -50.40, respectively;

$p < 0.05$) and for the 200 mg eluxadoline group at weeks 8 and 12 (-19.89, -27.48, respectively; $p < 0.05$). A greater improvement in QoL (IBS-QoL total score) was observed for patients receiving treatment with 100 and 200 mg eluxadoline when compared with placebo at the end of weeks 4, 8, and 12. Adequate relief was achieved in more patients who received

treatment with 100 or 200 mg eluxadoline at weeks 4, 8, and 12 (69.3%/67.4%, 74.9%/71.5%, 79.7%/75.4%, respectively; $p < 0.05$), and at week 8 in those receiving 25 mg eluxadoline when compared with placebo (64.2% vs 56.8%). Over the entire study duration, there was a statistically significant increase in the percentage of adequate relief responders in the 100 and 200 mg groups (63.5% and 59.3%, respectively) when compared with placebo (46.4%; $p < 0.05$).

Phase III studies included patients who received eluxadoline 100 or 75 mg twice daily, since the 200 mg twice-daily dose did not provide better risk–benefit ratio over the 100 mg dose.[38] IBS-3001 and IBS-3002 were reported in four papers, inclusive of a pooled analysis.[1,39–41] They are randomized, double-blind, placebo-controlled, parallel-group, multicenter studies involving overall 2,427 subjects being randomized to compare eluxadoline 75 or 100 mg twice daily and placebo. IBS-3001 was approximately 58 weeks, and IBS-3002 was approximately 34 weeks. A composite clinical response, defined as decrease in daily worst abdominal pain and Bristol Stool Scale scores over 26 weeks, was evaluated.[25] A patient was defined as a clinical responder if they met the daily response criteria for at least 50% of the days with diary entries. Treatment with 100 mg eluxadoline resulted in an absolute 9.1–13.7%-point increase in the proportion of patients achieving the composite primary end point when compared with placebo.[21] In both IBS-3001 and IBS-3002, a significantly greater proportion of patients receiving 100 mg eluxadoline met the primary end point of clinical response compared with placebo at week 26 (29.3% vs 20.2% and 32.7% vs 19.0%, respectively, $p \leq 0.001$). In IBS-3002, a significantly greater proportion of patients receiving 75 mg eluxadoline achieved a composite response compared with placebo (30.4% vs 20.2%, respectively, $p < 0.05$). A similar composite response was found in the pooled analysis with the treatment benefit of eluxadoline over placebo being maintained throughout weeks 1–26.[1] At week 26, there were significantly more adequate relief responders in those patients receiving 100 mg eluxadoline in both IBS-3001 and IBS-3002 when compared with placebo (49.5% vs 40.0% and 53.7% vs 43.7%, respectively, $p < 0.01$), with a similar pattern in the pooled analysis ($p < 0.05$), while IBS-3002 showed an effect for 75 mg eluxadoline as well, compared with placebo (52.8% vs 43.7%, respectively, $p = 0.013$). In IBS-3001, IBS-3002, and the pooled analysis, there was a significant increase in stool consistency responders in patients receiving 100 mg eluxadoline throughout weeks 1–26 (34.0% vs 24.1%, 39.8% vs 23.6%, 36.8% vs 23.9%, respectively, $p \leq 0.001$). IBS-3002 showed a significant effect of 75 mg

eluxadoline compared with placebo as well in stool consistency responders (34.4% vs 23.6%, $p < 0.001$).

In IBS-3001 and IBS-3002, there was no significant difference in the proportion of pain responders at 12 and 26 weeks in either eluxadoline groups vs placebo. The pooled analysis however managed to show an effect on pain in the 100 mg eluxadoline group vs placebo ($p < 0.05$), albeit the criteria were slightly more strict. IBS-QoL scores were generally higher in patients receiving 75 or 100 mg eluxadoline when compared with placebo from both studies and their pooled analysis. In a longitudinal analysis, scores were significantly higher than placebo for both eluxadoline treatment groups at each visit in IBS-3001 and in the 75 mg group in IBS-3002, while statistical differences were observed at 4, 8, 12, and 18 weeks in the 100 mg group in IBS-3002. In the pooled analysis, IBS-QoL total scores were significantly greater than placebo at week 26 for both the 75 and 100 mg treatment groups ($p < 0.001$). Finally, significant improvements were observed in abdominal bloating, abdominal discomfort, frequency of bowel movements, risk of urgency episodes, and risk of incontinence episodes in patients receiving treatment with eluxadoline compared with placebo.

Meta-analysis
Meta-analysis was performed on five outcomes at two time points, 12 weeks and 26 weeks: Bristol Stool Scale consistency score, Daily Pain Score, IBS-QoL Total Score, Global Symptom Score, and Adequate Relief of IBS Symptoms. The effects of eluxadoline are statistically significant for all outcomes in favor of eluxadoline, albeit a small-to-moderate effect. There was heterogeneity in the Bristol Stool Scale consistency at 12 weeks and the IBS-QoL at 26 weeks (Table 2 and Figure 3). Quality assessment was satisfactory with no bias present (Figure 4).

Safety and adverse events
Frequency of any adverse events ranged from 43.8% to 60.2% in all trials. Serious adverse events were between 3.0% and 4.8%, and no deaths were reported during the study. The frequency of adverse events was largely equal between placebo and treatment (Figure 5). Overall, eluxadoline was well tolerated with the most common adverse events being nausea, constipation, vomiting, and abdominal pain seen in patients with IBS-D (frequency less than 10%). The rate of discontinuation due to constipation and nausea was small and ranged between 0.6% and 1.7% for eluxadoline. Five (0.3%) patients receiving eluxadoline developed pancreatitis, and there were eight (0.5%) cases of abdominal pain with elevated levels of

Table 2 Meta-analysis of efficacy outcomes and main adverse events

Outcome	Studies	Participants	Effect estimate (95% CI)	Heterogeneity: I^2 (%)
Efficacy outcomes				
Bristol Stool Scale consistency score				
12 weeks[a]	3	1524	SMD: -0.29 (-0.45, -0.13)	56
26 weeks[a]	2	1057	SMD: -0.42 (-0.64, -0.20)	67
Daily Pain Score				
12 weeks[a]	3	1529	SMD: -0.17 (-0.27, -0.07)	0
26 weeks[a]	2	1060	SMD: -0.16 (-0.28, -0.04)	0
IBS-QoL Total Score				
12 weeks[a]	3	1581	SMD: 0.21 (0.11, 0.31)	10
26 weeks[a]	2	1128	SMD: 0.16 (0.04, 0.27)	31
Global Symptom Score				
12 weeks[a]	2	1287	SMD: -0.15 (-0.27, -0.04)	0
26 weeks[a]	2	1060	SMD: -0.14 (-0.27, -0.02)	0
Adequate Relief of IBS Symptoms				
12 weeks[b]	3	913	OR: 1.99 (1.61, 2.45)	2
26 weeks[b]	2	1060	OR: 1.78 (1.35, 2.35)	0
Adverse events				
All adverse events[c]	2	1991	OR: 1.02 (0.79, 1.32)	32
Constipation[c]	2	1991	OR: 3.49 (2.20, 5.55)	0
Vomiting[c]	2	1991	OR: 3.42 (1.79, 6.54)	0
Abdominal pain[c]	2	1991	OR: 1.78 (1.17, 2.70)	0
Nausea[c]	2	1937	OR: 1.42 (0.97, 2.07)	0

Notes: [a]SMD (inverse variance random effects). [b]OR (inverse variance random effects). [c]OR (Mantel–Haenszel random effects).
Abbreviations: IBS, irritable bowel syndrome; OR, odds ratio; QoL, quality of life; SMD, standardized mean difference.

hepatic enzymes in IBS-3001 and IBS-3002. Eight of the 13 cases were associated with spasm in the sphincter of Oddi (0.5%). All cases were associated with prior cholecystectomy, and seven cases occurred within 2 weeks of initiated study drug.[21] Other adverse events are summarized in Table 3. There was no evidence to suggest biochemical derangement, worsening of IBS symptoms or opioid withdrawal.[1,38–41]

Random-effects meta-analysis of the adverse events indicated that constipation and vomiting were up to 3.5 times more likely to occur with eluxadoline 100 mg compared with placebo. Nausea and abdominal pain were 42% and 78%, respectively, more likely to occur with eluxadoline 100 mg compared with placebo. Constipation, vomiting, and abdominal pain were significantly higher in the 100 mg eluxadoline group compared with placebo whilst adverse events overall and nausea were not. Significant heterogeneity was not present in any adverse event analyzed.

Discussion and conclusion

The current review looked at the characteristics of eluxadoline, a gut-targeting mu- and kappa-opioid receptor agonist and a delta-opioid receptor antagonist, and the clinical trials that investigated its efficacy and safety in IBS-D. Overall, eluxadoline is a new molecule with attractive characteristics for the patients with IBS-D, having shown efficacy in

improving stool consistency, global symptoms, IBS severity, QoL, pain, and adequate relief. Its main side effects include nausea, vomiting, constipation, and abdominal pain. Precautions should be taken when using it with respect to interaction with certain class of drugs and patients at risk of sphincter of Oddi spasm leading to pancreatitis. The overall quality of trials is satisfactory with the meta-analyses providing largely homogeneous outcomes.

Its place in clinical practice might prove useful since the pharmacological options of IBS-D are limited to loperamide, antispasmodics, and antidepressants. Less commonly used are 5-HT$_3$ receptor antagonists,[46] or rifaximin.[47] The evidence for antidepressants in IBS-D is limited,[48] while for loperamide or antispasmodics clinical experience is existent and accessibility to them is eased by low cost and over-the-counter purchasing. Clinical use will show whether eluxadoline might prove a suitable second-line treatment for IBS-D instead of antidepressants, or if it will function preferably as third line. A recent NICE UK technology review suggests that eluxadoline can be considered a cost-effective treatment for patients with IBS-D who have not responded adequately to or cannot tolerate other suitable pharmacological therapies.[21]

The current emerging treatments for IBS-D are rifaximin and selective 5-HT$_3$ receptors along with existing first-line treatments such as antispasmodics, loperamide, tricyclic
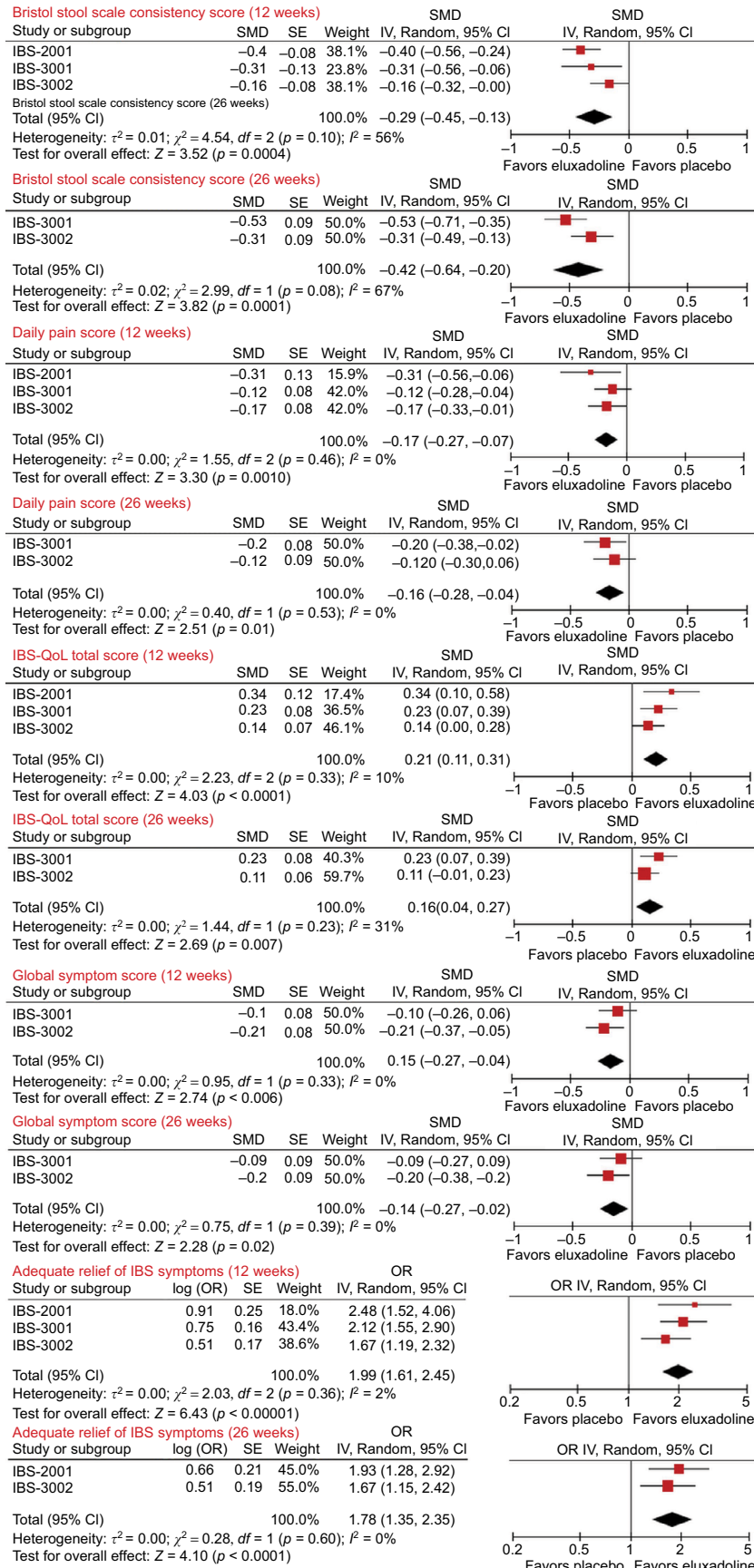
Figure 3 Forest plots of efficacy outcomes.
Note: Eluxadoline vs placebo at 12 and 26 weeks.
Abbreviations: IBS, irritable bowel syndrome; IV, inverse variance; OR, odds ratio; QoL, quality of life; SE, standard error; SMD, standardized mean difference.
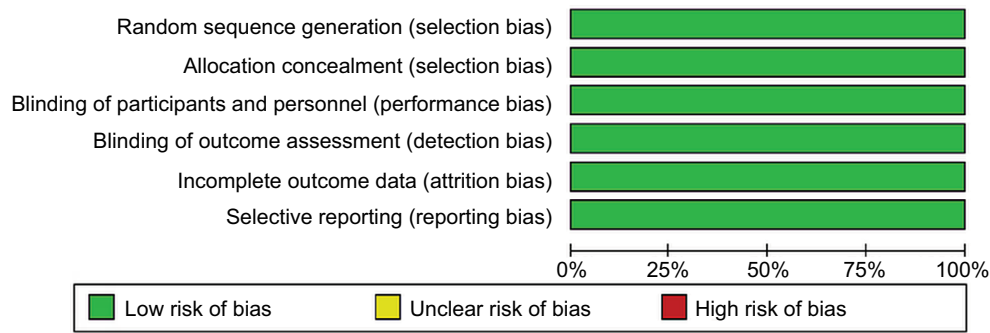
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)

0%   25%   50%   75%   100%

■ Low risk of bias   ■ Unclear risk of bias   ■ High risk of bias

Figure 4 Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.
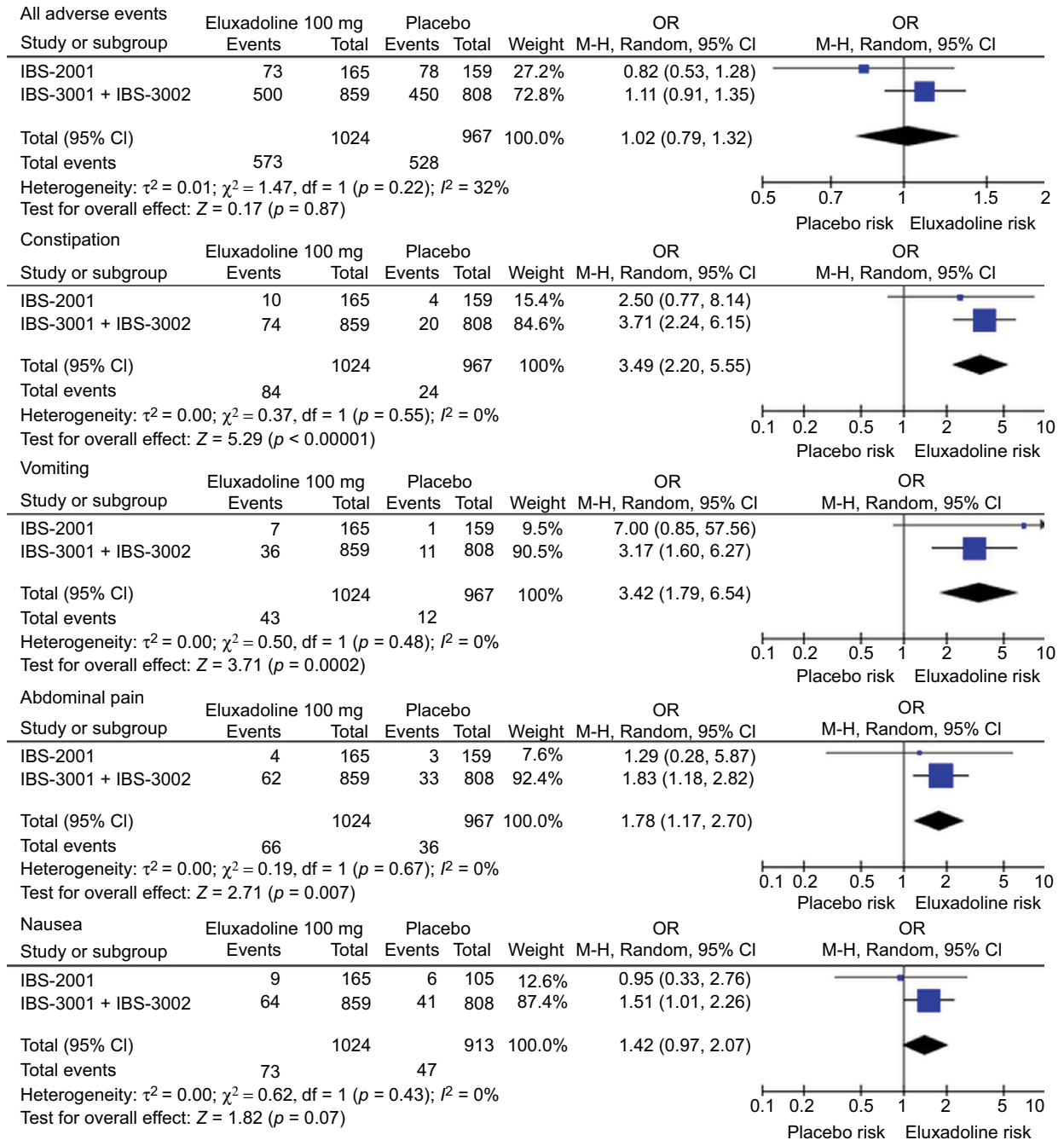
All adverse events

Study or subgroup	Eluxadoline 100 mg Events	Total	Placebo Events	Total	Weight	OR M-H, Random, 95% CI
IBS-2001	73	165	78	159	27.2%	0.82 (0.53, 1.28)
IBS-3001 + IBS-3002	500	859	450	808	72.8%	1.11 (0.91, 1.35)
Total (95% CI)		1024		967	100.0%	1.02 (0.79, 1.32)
Total events	573		528			

Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 1.47$, df = 1 ($p = 0.22$); $I^2 = 32\%$
Test for overall effect: $Z = 0.17$ ($p = 0.87$)

Constipation

Study or subgroup	Eluxadoline 100 mg Events	Total	Placebo Events	Total	Weight	OR M-H, Random, 95% CI
IBS-2001	10	165	4	159	15.4%	2.50 (0.77, 8.14)
IBS-3001 + IBS-3002	74	859	20	808	84.6%	3.71 (2.24, 6.15)
Total (95% CI)		1024		967	100%	3.49 (2.20, 5.55)
Total events	84		24			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.37$, df = 1 ($p = 0.55$); $I^2 = 0\%$
Test for overall effect: $Z = 5.29$ ($p < 0.00001$)

Vomiting

Study or subgroup	Eluxadoline 100 mg Events	Total	Placebo Events	Total	Weight	OR M-H, Random, 95% CI
IBS-2001	7	165	1	159	9.5%	7.00 (0.85, 57.56)
IBS-3001 + IBS-3002	36	859	11	808	90.5%	3.17 (1.60, 6.27)
Total (95% CI)		1024		967	100%	3.42 (1.79, 6.54)
Total events	43		12			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.50$, df = 1 ($p = 0.48$); $I^2 = 0\%$
Test for overall effect: $Z = 3.71$ ($p = 0.0002$)

Abdominal pain

Study or subgroup	Eluxadoline 100 mg Events	Total	Placebo Events	Total	Weight	OR M-H, Random, 95% CI
IBS-2001	4	165	3	159	7.6%	1.29 (0.28, 5.87)
IBS-3001 + IBS-3002	62	859	33	808	92.4%	1.83 (1.18, 2.82)
Total (95% CI)		1024		967	100.0%	1.78 (1.17, 2.70)
Total events	66		36			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.19$, df = 1 ($p = 0.67$); $I^2 = 0\%$
Test for overall effect: $Z = 2.71$ ($p = 0.007$)

Nausea

Study or subgroup	Eluxadoline 100 mg Events	Total	Placebo Events	Total	Weight	OR M-H, Random, 95% CI
IBS-2001	9	165	6	105	12.6%	0.95 (0.33, 2.76)
IBS-3001 + IBS-3002	64	859	41	808	87.4%	1.51 (1.01, 2.26)
Total (95% CI)		1024		913	100.0%	1.42 (0.97, 2.07)
Total events	73		47			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.62$, df = 1 ($p = 0.43$); $I^2 = 0\%$
Test for overall effect: $Z = 1.82$ ($p = 0.07$)

Figure 5 Forest plots of adverse events.
Note: Eluxadoline 100 mg vs placebo.
Abbreviations: M-H, Mantel–Haenszel; OR, odds ratio.

Table 3 Frequency of adverse events for IBS-2001, IBS-3001, and IBS-3002

Adverse events	Pooled analysis of IBS-3001 and IBS-3002				IBS-2001				
	Eluxadoline			Placebo (n = 808)	Eluxadoline				Placebo (n = 159)
	75 mg (n = 807)	100 mg (n = 859)	Combined groups (n = 1,666)		5 mg (n = 105)	25 mg (n = 170)	100 mg (n = 165)	200 mg (n = 172)	
All adverse events	486 (60.2)[a]	500 (58.2)	986 (59.2)	450 (55.7)	46 (43.8)	86 (50.6)	73 (44.2)	90 (52.3)	78 (49.1)
Serious adverse events	34 (4.2)	41 (4.8)	75 (4.5)	24 (3.0)					
Cardiac events	12 (1.5)	17 (2.0)	75 (4.5)	8 (1.0)					
Pancreatitis	2 (0.2)	3 (0.3)	5 (0.3)	0 (0.0)					
Spasm of the sphincter of Oddi	1 (0.1)	7 (0.8)	8 (0.5)	0 (0.0)					
Constipation	60 (7.4)	74 (8.6)	134 (8.0)	20 (2.5)	2 (1.9)	5 (2.9)	10 (6.1)	6 (3.5)	4 (2.5)
Nausea	65 (8.1)	64 (7.5)	129 (7.7)	41 (5.1)	6 (5.7)	11 (6.5)	9 (5.5)	18 (10.5)	7 (4.4)
Abdominal pain	47 (5.8)	62 (7.2)	109 (6.5)	33 (4.1)	3 (2.9)	6 (3.5)	4 (2.4)	13 (7.6)	3 (1.9)
Vomiting	32 (4.0)	36 (4.2)	68 (4.1)	11 (1.4)	1 (1.0)	7 (4.1)	7 (4.2)	12 (7.0)	1 (0.6)
Abdominal distension	21 (2.6)	22 (2.6)	43 (2.6)	13 (1.6)	0 (0.0)	0 (0.0)	6 (3.6)	1 (0.6)	2 (1.3)
Gastroenteritis	36 (4.5)	19 (2.2)	55 (3.3)	27 (3.3)					
Flatulence	21 (2.6)	27 (3.1)	48 (2.9)	13 (1.6)					
Upper respiratory tract infection	27 (3.3)	47 (5.5)	74 (4.4)	32 (4.0)					
Bronchitis	26 (3.2)	27 (3.1)	53 (3.2)	18 (2.2)	4 (3.8)	4 (2.4)	3 (1.8)	1 (0.6)	3 (1.9)
Sinusitis	27 (3.3)	24 (2.8)	51 (3.1)	26 (3.2)	5 (4.8)	4 (2.4)	3 (1.8)	1 (0.6)	9 (5.7)
Nasopharyngitis	33 (4.1)	23 (2,7)	56 (3.4)	27 (3.3)	4 (3.8)	8 (4.7)	7 (4.2)	6 (3.5)	6 (3.8)
Dizziness	21 (2.6)	28 (3.3)	49 (2.9)	17 (2.1)					
Anxiety	10 (1.2)	19 (2.2)	29 (1.7)	14 (1.7)					
Increased level of alanine aminotransferase	17 (2.1)	26 (3.0)	43 (2.6)	12 (1.5)					

Note: [a]Number of patients (%).
Abbreviation: IBS, irritable bowel syndrome.

antidepressants, and selective serotonin reuptake inhibitors. A statistical comparison of the outcomes for eluxadoline against other treatments is not possible without a network meta-analysis, but a narrative comparison can provide some insight. It has been reported that the number needed to treat for selective serotonin reuptake inhibitors or tricyclic antidepressants was four in IBS-D,[49,50] which is lower than the number needed to treat for eluxadoline from the current review (9 [95% CI: 7–13] at 12 weeks, 17 [95% CI: 11–32] at 26 weeks to achieve adequate relief). Rifaximin is the antibiotic mostly evaluated in studies with patients with IBS. It is an oral, non-absorbable, broad-spectrum antibiotic targeting gut flora and has been shown to relieve IBS symptoms, bloating, abdominal pain, and loose or watery stools better than the placebo for up to 10 weeks after completion of therapy with repeat courses not hindering its durability.[51] Alosetron and ondansetron as selective 5-HT[3] receptors have also shown promise in improving stool consistency, improving pain (mainly alosetron), and prolonging gut transit. Compared with eluxadoline, durability was one aspect that was not maintained and declined at 26 weeks while gut transit was not examined or reported in eluxadoline studies.

Despite the statistical significance of the current review's results, caution should be exercised as to how to extrapolate these results to clinically meaningful improvements. The SMDs for pain, QoL, global symptoms score, and stool consistency were generally low to moderate. The most relevant clinical figure of the results is the OR for adequate relief which indicated that almost twice as many responders were in the eluxadoline group, reflecting the numbers needed to treat mentioned earlier. What is apparent is that eluxadoline's response over time declines with regard to almost all symptoms (pain, stool consistency, global symptoms, and adequate relief).

Next, the side effects of eluxadoline are an additional reason that support its use as a third-line treatment. Considering the increased frequency of cholecystectomies in populations,[52,53] the prospect of acute pancreatitis with consequent hospitalizations is very serious and could deter use. Furthermore, the presence of side effects such as constipation or nausea might well be considered as bad as the original symptoms of IBS-D. Patients might have increased visceral hypersensitivity, and in the context of having failed other treatments already they might be apprehensive trying further medications if they know the high possibility of side effects.

A final point that needs to be considered is the potential for opioid abuse with eluxadoline as a mu- and kappa-opioid receptor agonist. This was shown with the presence of euphoric mood, drunkenness, or sedation, as an adverse event and the general recommendation that patients need to be monitored for their ability to drive a car when on treatment. No other central nervous system side effects were noted outside these events. The data so far however allow a reserved view of eluxadoline as a drug with a low potential for abuse and low risk of dependence, with the US Drug Enforcement Administration (DEA) having ruled that eluxadoline be placed into Schedule IV of the Controlled Substances Act. This is due to the fact that adverse events of euphoric mood were observed with both oral and intranasal eluxadoline at a much lower frequency compared with oxycodone, similar rates of euphoric mood were noted with eluxadoline and placebo and there was also no evidence of opioid withdrawal after discontinuation of eluxadoline. Similarly, the peripheral mu-opioid receptor agonist loperamide showed evidence of limited abuse potential in clinical studies and is not a drug of abuse.[54] The potential for abuse could stem from the delta-receptor selective antagonism as has been exhibited in mice.[34,55,56] Pharmacovigilance with prospective follow-up of self-administration or human trials will be required to determine whether eluxadoline is in fact subject to abuse.

In conclusion, considering its affinity to mu-opioid receptors, it is interesting to see whether eluxadoline's use will be investigated in other cases of functional diarrhea such as diabetic diarrhea, opioid withdrawal-induced diarrhea, fecal incontinence, or even high ostomy outputs. The potential for abuse needs to be carefully monitored by clinicians and the pharmaceutical industry. Nevertheless, eluxadoline will hopefully prove successful in filling the treatment gap currently present in IBS-D.

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Disclosure

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