SPECIAL ARTICLE

Eluxadoline in the treatment of diarrhea-predominant irritable bowel syndrome. The SEPD perspective

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ABSTRACT

Functional gut disorders, including diarrhea-predominant irritable bowel syndrome, are highly prevalent conditions worldwide that significantly impact health economy and patient quality of life, yet lacking fully satisfactory therapeutic options. These circumstances fostered research on various molecules with more specific therapeutic targets, including opioid receptors. Eluxadoline (Allergan's Vibercy® in the USA, Truberzi® in Europe) is a locally-acting mixed µ- and κ-opioid receptor agonist, and δ-opioid receptor antagonist, that was licensed in 2015 by the Food and Drug Administration (FDA) and in 2016 by the European Medicines Agency (EMA) for use in diarrhea-predominant irritable bowel syndrome. Eluxadoline provides, with advantage over the current standard of care, control of both stool consistency and abdominal pain, good tolerability in most cases, and improved quality of life, hence it deserves consideration when approaching a patient with this disorder. As with any recently approved therapy, adequate pharmacovigilance is to be expected, as well as studies to inform on different scenarios such as on-demand therapy, loss of response assessment, use as rescue therapy for other molecules, and cost-effectiveness, to further characterize and more accurately position eluxadoline within the therapeutic spectrum.

Key words: Irritable bowel syndrome. Diarrhea. Eluxadoline. Opioid receptors.

BACKGROUND, JUSTIFICATION, AND POTENTIAL CONFLICTS OF INTEREST

Functional gut disorders, including diarrhea-predominant irritable bowel syndrome (IBS-D), are highly prevalent conditions worldwide that significantly impact health economy and patient quality of life (1), yet lacking fully satisfactory therapeutic options. This prompted research on various molecules with more specific therapeutic targets, including opioid receptors. These receptors are found both in the central nervous system and the enteric nervous system, and play a role in both visceral sensitivity and gut motility control (2).

Eluxadoline (Allergan, Vibercy®, in the USA; Truberzi® in Europe) is a µ-opioid receptor agonist and δ-opioid receptor antagonist, with yet non-fully characterized agonist activity on κ-opioid receptors, that was licensed in May 2015 by the FDA and then, in September 2016, by the EMA for use in diarrhea-predominant irritable bowel syndrome (3-5). Eluxadoline reduces pain and improves stool consistency for patients with this condition with a favorable safety profile (6).

The Sociedad Española de Patología Digestiva (SEPD) is a non-profit scientific and professional organization whose primary goal is the fostering and dissemination of research and knowledge in the field of digestive system diseases.

It is in this setting that the present perspective article was developed, at the request of the SEPD President, to provide an independent, objective scientific analysis on the opportunity of introducing eluxadoline in Spain for the management of patients with IBS-D.

CLINICAL FRAME OF APPLICATION

Irritable bowel syndrome (IBS) is a highly prevalent functional disorder. It is estimated to involve 10% of the Spanish general population (7). It represents a major reason for care-seeking within our specialty (8), but remains nevertheless an underdiagnosed disorder. It has a chronic, intermittent course characterized by abdominal pain in association with changes in stool frequency and/or consistency (9). Identification and management are challenging in clinical practice, and require adequate coordination amongst care levels (10).

IBS diagnostic criteria have evolved over the years, and are based on symptoms and time-related criteria that allow the identification of patients with IBS in clinical practice. These patients undergo a minimum of lab tests to rule out any organic conditions on a case-by-case basis. The prior Rome III criteria (11) have been recently replaced by the current Rome IV ones (12), which are less restrictive and

more applicable in clinical practice: they not only require that pain be improved by defecation but also that pain be modified by or related to defecation. Similarly, symptom timing is also less restrictive, and symptom onset falls now within six months before diagnosis rather than 12 months before diagnosis, as was the case with the prior criteria. Symptoms include recurrent abdominal pain, at least one day weekly on average for the past three months, with symptom onset within six months before diagnosis, in association with two or more of the following criteria: pain related to defecation, with changes in stool frequency or consistency. Stool consistency, according to the Bristol Stool Form Scale (BSFS), allows IBS subtype (constipation-predominant, diarrhea-predominant, mixed-type, unclassified) to be established (13).

A review of the literature on the psychosocial impact of IBS reveals the condition has a major impact on quality of life (14).

The cause of this disorder remains unknown, but significant insights have been gained into its pathophysiology, which involves both genetic and environmental factors that might potentially alter intestinal permeability thus inducing micro-inflammatory changes, which in turn might alter motility, secretion, and visceral sensitivity. Specifically, for diarrhea-predominant IBS, changes in intestinal permeability have been reported (15). Symptoms, then, seemingly result from a complex interaction between microbiota dysbiosis, immune dysfunction at the intestinal mucosa, changes in visceral hypersensitivity, and impaired intestinal and motor modulation by the central nervous system.

In IBS-D, a highly prevalent IBS subtype, multiple therapy targets have been used involving non-absorbable antibiotics such as rifaximin and probiotics, with limited benefits over placebo (16-18), and intestinal motility inhibitors such as loperamide, with rapidly reduced bowel movements as compared to placebo but an increase in abdominal pain (19,20) and severe constipation as adverse effects. With other motility inhibitors such as the 5-hydroxytryptamine 3 (5-HT3) receptor (21) antagonists alosetron and cilansetron improvements were reported for symptoms, stool consistency, and quality of life *versus* placebo in women with severe IBS-D (22). However, alosetron was voluntarily withdrawn because of reports involving ischemic colitis events, only to be later reintroduced into the US market under restrictive conditions. Cilansetron failed to complete its development, and was not licensed by the FDA or the EMA. Furthermore, ramosetron also showed short-term symptom improvements over placebo with a good safety profile (23). However, it is marketed only in Asia (Japan, India). A phase II study of the tryptophan inhibitor LX-1031 demonstrated decreases in peripheral serotonin synthesis and stool consistency normalization, but no follow-up was reported (24). Nevertheless, no significant differences *versus* placebo were found for abdominal pain control.

Opioid receptors (μ, δ, κ) represent another recently selected therapy target; they bind endogenous opioid peptides that would presumably control intestinal motility and secretion. Specifically, μ-opioid receptor agonists inhibit small-bowel peristalsis, thus delaying transit through the small and large intestines, and increase basal sphincter pressure, among other effects (25).

From all the above, rifaximin and probiotics, with a very limited edge over placebo, as well as the other gradually withdrawn drugs, either failed to be licensed or stopped their clinical development, in addition to providing no overall improvement on the condition (they only treated diarrhea); hence, there is currently a therapeutic void for patients with IBS-D.

Eluxadoline is then developed with a dual action profile as μ-opioid agonist and δ-opioid antagonist, and an effective action against diarrhea and pain.

Eluxadoline is administered orally at a dose of 100 mg or 75 mg, according to patient needs. With 100 mg plasma concentration is very low (C_{max} 2-4 ng/ml, area under curve (AUC) 12-22 ng-h/ml). It is rapidly absorbed, with a peak concentration after 1.5-2 hours. Fat-rich foods considerably reduce C_{max} (2).

Eluxadoline is excreted primarily in the feces, and less than 1% in the urine. Mean plasma elimination half-life is 3.7-6 hours.

Administering eluxadoline to patients with impaired liver function (e.g., cirrhosis), or administering it together with potent P450 cytochrome inhibitors and organic anion transporting polypeptides (OATP1B1), may increase drug exposure. Extra precautions should be taken with these patients (3,4).

CLINICAL STUDIES SUPPORTING THE USE OF ELUXADOLINE

Preclinical studies

Eluxadoline was assessed in a murine model of induced stress where it improved intestinal transit. Eluxadoline normalized stool production, which had increased with stress induction, using a dose range of 5 to 100 mg/kg. (26). In a rat model of visceral hypersensitivity, using a pressure balloon as a measure of pseudoaffective response, eluxadoline 50 mg/kg achieved an antihyperalgesic effect from baseline within 30 minutes.

In another study assessing the drug's mode of action, eluxadoline and loperamide effects were comparatively analyzed in wild-type (WT) and delta receptor knock-out mice (27); eluxadoline was more effective to reduce diarrhea in WT mice where the condition had been induced using castor oil, which verified both its μ-opioid agonist (in the absence of δ-opioid receptors) properties and its dual action as μ-opioid/δ-opioid heteromer.

Clinical studies

Phase 2

A phase 2 randomized, double-blind, placebo-controlled study assessed the efficacy, safety and tolerability of eluxadoline over 12 weeks in 807 patients of both genders who met the Rome III criteria (28). Patients who daily had stool consistency ≥ 5.5 according to the BSFS (1 = hard feces, 7 = liquid feces), and with abdominal pain worsening ≥ 3 according to the worst abdominal pain (WAP) scale (0 = no pain, 10 = worst pain imaginable) were included. Patients were randomized to receive eluxadoline twice daily (5, 25, 100, or 200 mg) or placebo. The primary endpoint was the percentage of patients achieving clinical response at week 4, defined as a reduction in abdominal pain > 30% from baseline and a reduction of at least two points in the pain scale (0-10), as well as a BSFS score of 3 or 4 in at least 66% of days.

The primary endpoint was achieved in 12.4%, 12%, 11%, and 13.8% of patients randomized to eluxadoline 5, 25, 100, and 200 mg, respectively, *versus* 5.7% in the placebo arm; differences *versus* placebo were significant for all doses except 100 mg. However, at week 12 the group receiving 100 mg did reach statistical significance over placebo (20.2% *vs* 11.3%; p = 0.030). Symptom relief was significantly superior with eluxadoline 100 mg and 200 mg as compared to placebo (p = 0.02 and 0.023, respectively). Stool frequency and urgency (secondary endpoints) were reduced in the eluxadoline arm *versus* placebo (Table 1).

A *post-hoc* analysis of the primary endpoint showed that 28% of patients on the 100-mg dose, and 28.5% of those on the 200-mg dose, had reached said response during the trial's 12 weeks *versus* 13.8% on placebo (p = 0.002 for both doses).

Adverse effects were similar in all groups except for the eluxadoline 200-mg arm, where events were higher and led to drug discontinuations for non-serious digestive and neurological toxicities. No clear dose-dependent tendency was observed, but serious adverse events leading to discontinuation and non-serious adverse events gastrointestinal or neurological in nature were more common in the 200-mg group. Most of the commonly reported events during the trial occurred in the 200-mg group (a dosage ultimately not marketed). Overall, most common adverse events included constipation (52%), nausea (10%), abdominal pain (8%), and vomiting (7%). Five patients discontinued treatment for constipation (four in the 200-mg group, only in the phase 2 study, and one in the placebo group). Three cases of acute pancreatitis were identified on-therapy, all in the eluxadoline group (two with 200 mg, one with 25 mg). All events were rapidly solved without sequelae. Of these three cases, one was associated with high alcohol blood levels and a history of hospital admission for alcoholic pancreatitis within two months prior to study onset. A fourth case of transient acute pancreatitis was identified 15 days after the last dose of eluxadoline 100 mg, while receiving clarithromycin for bronchitis.

Phase 3

Based on the efficacy and safety results of the above phase 2 study (28), two eluxadoline doses were selected for two phase 3 prospective, randomized, double-blind, placebo-controlled studies (IBS-3001, *ClinicalTrials.*

Table 1. Efficacy results from phase II and III studies of eluxadoline

Study	n	Time	Dose (mg)	Primary endpoint clinical response*/ placebo week 4	p	Primary endpoint clinical response*/ placebo week 12	p	Primary endpoint clinical response*/ placebo week 26	p	Secondary endpoints (frequency, stools, urgency)
Phase 2 (22)	807	12 w	5	12.4%-5.7%	ns	-	-	-	-	ns
			25	12%-5.7%	0.041	-	-	-	-	ns
			100	11%-5.7%	ns	-	-	-	-	20.2-11.3 (p < 0.05)
			200	13.8%-5.7%	0.015	-	-	-	-	ns
Phase 3 (23) IBS-3001	1,282	26 w	75	-	-	23.9-17.1	0.01	23.4-19	ns	30-22 (p = 0.008)
			100	-	-	25.1-17.1	0.004	29.3-19	< 0.001	34-21 (p < 0.001)
IBS-3002	1,146	52 w	75	-	-	18.9-16.2	< 0.001	30.4-20.2	< 0.001	37-21 (p ≤ 0.001)
			100	-	-	29.6-16.2	< 0.001	32.7-20.2	< 0.001	36-21 (p ≤ 0.001)
			Placebo	-	-					

Primary endpoint: clinical response*, defined as a reduction in abdominal pain > 30% from baseline, with at least a reduction of two points in a pain scale, and a BSFS score of 3 or 4 in at least 66% of days. In the phase II study, clinical response was assessed at week 4, whereas in phase III studies response was assessed at weeks 12 and 26.

gov record NCT01553591; IBS-3002, *ClinicalTrials.gov* record NCT01553747) (6,29). The same inclusion criteria were used: BSFS ≥ 5.5, worsening of daily abdominal pain as measured with WAP ≥ 3, and an additional measurement of overall symptoms (Global Symptom Score [GSS]) as related to diarrhea-predominant irritable bowel syndrome (IBS-D): GSS ≥ 2 (0 = no symptoms associated with IBS-D; 4 = severe symptoms associated with IBS-D). Patients with a history of pancreatitis, sphincter of Oddi dysfunction, post-cholecystectomy pain, and alcohol abuse were excluded.

Patients were randomized to receive eluxadoline 75 or 100 mg *versus* placebo for 26 weeks. In the IBS-3001 study, patients underwent an additional 26-week period of double-blind treatment to assess eluxadoline safety, followed by two more weeks following drug discontinuation. In the IBS-3002 study, a four-week, single-blind period with placebo followed the 26-week period of treatment.

The primary endpoint included a composite of improved abdominal pain (30% or greater reduction in baseline WAP in ≥ 50% of days) and improved stool consistency (mean BSFS < 5) at week 12 (as requested by the FDA) and week 26 (as requested by the EMA). Secondary endpoints included improved abdominal pain, improved stool consistency, improved frequency of bowel movements, and improved GSS response.

A total of 2,428 patients were included in both studies (1,282 in IBS-3001, 1,146 in IBS-3002). An intent-to-treat (ITT) analysis was performed in 2,425 patients (1,280 from IBS-3001, 1,145 from IBS-3002). With the follow-up suggested by the FDA, the patients in the eluxadoline 75 mg/12 h group had a significantly superior response as compared to placebo during weeks 1-12 (23.9% *vs* 17.1% in IBS-3001, p = 0.01; 28.9% *vs* 16.2% in IBS-3002, p < 0.001). The same was the case with patients who received 100 mg/12h *versus* placebo during weeks 1-12 (25.1% *vs* 17.1% in IBS-3001, p = 0.004; 29.6% *vs* 16.2% in IBS-3002, p < 0.001).

At 26 weeks, the cut-off suggested by the EMA, the response rate *versus* placebo for 100 mg/12h was 29.3% *vs* 19%, and 32.7% *vs* 20.2%, respectively, in IBS-3001 and IBS-3002 (p < 0.001 in both studies). In the IBS-3002 study significant differences *versus* placebo were indeed found for 75 mg/12 h (30.4% *vs* 20.2%, p < 0.001), not so in IBS-3001 with this dosage. Both with 100 mg and 75 mg significant differences *versus* placebo were seen for the secondary endpoints of improved stool consistency and frequency (Fig. 1 and Table 1).

Side effects were comparable to those of placebo with both 75 and 100 mg. Most common adverse events included constipation (7% for 75 mg, 8% for 100 mg), nausea (8% for 75 mg, 7% for 100 mg), and abdominal pain (7% for both doses). However, the proportion of drug discontinuations for constipation was not significantly different *versus* placebo (1.1, 1.7, and 0.2% with eluxadoline 75 mg, 100 mg, and placebo, respectively).
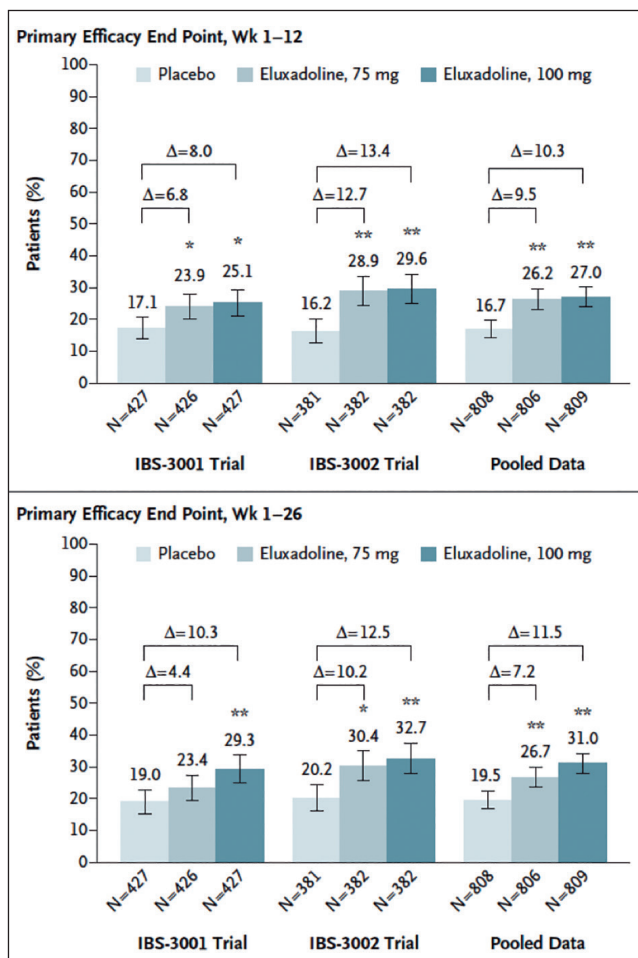

Fig. 1. Phase-III clinical trial results of eluxadoline 75 or 100 mg versus placebo in the IBS-3001 and IBS-3002 studies. Reproduced (6) with permission from the Massachusetts Medical Society. The *New England Journal of Medicine*, Lembo AJ et al., *Eluxadoline for irritable bowel syndrome with diarrhea*, volume 374, page 248. Copyright© (2016) Massachusetts Medical Society.
Primary endpoint: proportion of patients achieving a ≥ 30% reduction from baseline of abdominal pain, as measured by a worst abdominal pain (WAP) score in almost 50% of evaluation days, and < 5 in a stool consistency score in those same days, over 1-12 weeks in the upper panel and 1-26 weeks in the lower panel. *= p < 0.05; **= p < 0.001.

There were five cases of pancreatitis in the eluxadoline group (0.2% for 75 mg, 0.3% for 100 mg). None of these led to organ failure or to either local or systemic complications, and all five subsided within a week. All these patients had biliary changes (sphincter of Oddi spasms, bile sludge) or alcohol abuse (three of five cases).

The risk of habituation to this therapy was subsequently assessed in patients included in phase 2 and phase 3 studies, and no differences in withdrawal symptoms were found between eluxadoline and placebo (30).

VALIDITY AND CLINICAL APPLICABILITY OF THE RESULTS OBTAINED

Eluxadoline improves both abdominal pain and stool consistency in patients with IBS-D without inducing significant constipation in contrast to other antiperistaltic drugs.

Eluxadoline offers similar efficacy when compared to 5-HT3 antagonists for the management of IBS-related diarrhea. However, pain control is superior with eluxadoline, as the results from phase 2 and 3 studies reflect (Table 1). Furthermore, 5-HT3 antagonists cannot be currently considered as a therapy option given their absence from the Spanish market.

Constipation, a most relevant side effect for patients with increased visceral sensitivity, is less of an issue when compared to other medications such as loperamide, which are used for associated diarrhea but are not specifically indicated in IBS-D (because of no effect on abdominal pain). Furthermore, this drug seems to induce no withdrawal syndrome with any of the dosages assessed.

Also, improved quality of life may represent a milestone with this molecule, as patients suffering from IBS-D usually present with concomitant depression and anxiety.

Based on the results from pivotal phase 3 studies, the EMA recommends that therapy be generally initiated with 100 mg BID, at breakfast and dinner (31). For patients intolerant of 100 mg and those with mild-moderate liver impairment, 75 mg BID, at breakfast and dinner, is recommended. Both these doses have been marketed in Europe. Both the EMA, in the Summary of Product Characteristics (32), and the FDA, from March 2017 (33) following a revision of the original 2015 conditions of use, currently recommend that eluxadoline not be used in cholecystectomized individuals.

Since pancreatitis development (0.3%) and altered transaminases (0.5%) are both uncommon events, routine radiographic studies before eluxadoline onset does not seem to be a cost-effective measure (30). Notwithstanding, in addition to the contraindication for cholecystectomized individuals, the drug is also contraindicated in cases of potential bile duct obstruction or sphincter of Oddi dysfunction, in patients on potent inhibitors of OATP1B1 (e.g., cyclosporine), and in patients with a history of pancreatitis or liver dysfunction. Similarly, extra precautions should be taken in alcohol-drinking patients, and its use should be excluded in severe drinkers. Finally, the drug should be discontinued in the presence of severe constipation to prevent the risks associated with potential bowel obstruction.

The ability of eluxadoline to control not only abdominal pain but also stool consistency in contrast to other molecules makes this medication an attractive option for use in IBS-D.

However, as with any recently developed therapy, studies providing further information on certain scenarios are still lacking, which prevent us to accurately position eluxadoline in the therapeutic armamentarium. Such scenarios include on-demand therapy, loss of response assessment, use as rescue for other molecules, and cost-effectiveness estimation. Consequently, its use should be considered on a case by case basis, also as potential rescue therapy for conventional treatment failures or as first-line option for severe patients.

CONCLUSION

Eluxadoline, as compared to the other products used for IBS-D, provides control both of stool consistency and abdominal pain, with good tolerability in most cases, and improves quality of life for IBS patients, thus being a molecule deserving consideration in the management of IBS-D.

ACKNOWLEDGEMENTS

CONFLICTS OF INTEREST STATEMENT

The undersigned act on behalf of the Sociedad Española de Patología Digestiva (SEPD) to provide a review perspective on a new drug in the process of being incorporated into the therapeutic arsenal. Neither the SEPD nor any of the authors have links whatsoever with the companies developing drugs for IBS-D in general, or with Allergan, the company marketing eluxadoline in Spain, in particular. Neither the SEPD nor any of the authors hold financial interests in the companies that researched such drugs, albeit they maintain an ongoing relationship with said companies for education, research, and improved clinical practice purposes in the promotion of digestive health. Finally, both the SEPD and the undersigned authors declare that the development of the present report was completed independently of third parties both during the preliminary discussions and the final writing of its contents, which were revised by the SEPD before effective publication in the *Revista Española de Enfermedades Digestivas*.

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