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CADTH COMMON DRUG REVIEW

Clinical Review Report

ELUXADOLINE (VIBERZI)

(Allergan Pharma Co.)

Indication: For the treatment of Irritable bowel syndrome with diarrhea (IBS-D) in adults.

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Abbreviations

BSS	Bristol stool scale
CDR	CADTH Common Drug Review
CI	confidence interval
DB	double-blind
EMA	European Medicines Agency
FBD	functional bowel disease
GI	gastrointestinal
IBS	Irritable bowel syndrome
IBS-AR	adequate relief of Irritable bowel syndrome symptoms
IBD-C	Irritable bowel syndrome with predominant constipation
IBS-D	Irritable bowel syndrome with predominant diarrhea
IBS-M	Irritable bowel syndrome with mixed bowel habits
ICC	intraclass correlation coefficient
ITT	Intention to treat
IVRS	interactive voice response system
MCID	minimal clinically important difference
OR	odds ratio
QoL	quality of life
SD	standard deviation
SE	standard error
SOWS	Subjective Opiate Withdrawal Scale
WAP	worst abdominal pain

Drug	Eluxadoline (Viberzi)
Indication	For the treatment of Irritable bowel syndrome with diarrhea (IBS-D) in adults
Reimbursement Request	As per indication
Dosage Form	75 mg and 100 mg oral tablets
NOC Date	January 26, 2017
Manufacturer	Allergan Pharma Co.

Executive Summary

Introduction

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder associated with changes in the stool consistency, bowel habits, and symptoms of abdominal discomfort/pain and bloating. Based on the predominant stool consistency, a diagnosis of IBS can be classified into IBS with predominant diarrhea (IBS-D), IBS with predominant constipation (IBS-C), or IBS with mixed bowel habits. IBS-D is mainly characterized by the passage of loose stool. Also commonly present is an abnormal frequency of defecation (more than two bowel movements per day). The diagnosis of IBS is based on the exclusion of certain organic diseases and the presence of symptoms of pain associated with a change in bowel habits and stool consistency as described in Rome diagnostic criteria. The prevalence of IBS in Canada was reported as 5.7%, of which 35% are of the IBS-D subtype. Treatment of IBS-D follows a step-wise approach of dietary and lifestyle changes, psychological and behavioural therapy, and pharmacological treatment, which commonly involves antidiarrhea, antispasmodic, and antidepressant medications, none of which is approved by Health Canada for the treatment of IBS-D.

Eluxadoline (Viberzi) is a mixed mu opioid receptor agonist and delta opioid receptor antagonist indicated for the treatment of IBS-D in adult patients, approved by Health Canada to be given orally at a dosage of 100 mg twice daily. A reduced dose of 75 mg is recommended for geriatric patients or patients who cannot tolerate the 100 mg dose. Rare but serious adverse events reported in the product monograph are sphincter of Oddi spasms and pancreatitis.

The objective of this review is to perform a systematic review of the beneficial and harmful effects of eluxadoline for the treatment of IBS-D in adults.

Results and Interpretation

Included Studies

Two phase III, double-blind, randomized, placebo-controlled, parallel-group trials were included in the CADTH Common Drug Review (CDR) systematic review (IBS-3001 and IBS-3002). Patients with IBS-D (as diagnosed per Rome III criteria) were randomized (N = 1,281, IBS-3001; N = 1,146, IBS-3002) in a 1:1:1 ratio to 75 mg twice-daily eluxadoline, 100 mg twice-daily eluxadoline, and placebo groups. The primary outcome of both studies was a composite of worst abdominal pain score and stool consistency responders during the interval of one to 12 weeks (FDA end point requirement) or one to 26 weeks (European Medicines Agency end point requirement). Both studies were identical in design except that IBS-3001 included an additional 26 weeks of double-blind treatment with a subsequent two weeks of follow-up, while IBS-3002 included an additional four weeks of a single-blinded withdrawal period. All efficacy outcomes were reported at either 12 weeks or 26 weeks. Irritable Bowel Syndrome Quality of Life questionnaire (IBS-QoL) results were further reported at the end visit of each of the studies.

A key limitation of the included studies was a high percentage of patients discontinuing in both studies. IBS-3001 reported the percentage of patients who discontinued the study at 40.1%, 39.4%, and 37.0% in the 75 mg eluxadoline group, 100 mg eluxadoline group, and placebo groups, respectively. IBS-3002 reported the percentage of patients who discontinued the study at 34.4%, 31.1%, and 28.5% in the 75 mg eluxadoline group, 100 mg eluxadoline group, and placebo groups, respectively. Discontinuation rates in the eluxadoline groups were higher than in the placebo groups. Additionally, the clinical expert identified the outcomes used in the studies as not commonly used in clinical practice, and the lack of adjustment for multiple testing on outcomes other than the primary outcome, such as urgency episodes, abdominal discomfort scores, and bowel frequency, which showed statistical significance at 0.05, may introduce inflated type I error.

No direct or indirect comparisons between eluxadoline and any commonly used pharmacological drugs in the treatment of IBS-D were available. This represents a gap in the evidence as we are unable to determine the added clinical efficacy of eluxadoline against commonly used pharmacological drugs (i.e., off-label, antidiarrhea therapies such as loperamide) in the treatment of IBS-D symptoms.

Efficacy

The composite primary outcome defined a responder as a patient who achieved a responder status for both worst abdominal pain and stool consistency. For each component, the patient had to have had reported improvement of 30% or more compared with prescreening on 50% or more of the days in the interval of interest. In IBS-3001, 23.9% of patients in the 75 mg eluxadoline group and 25.1% in the 100 mg eluxadoline group achieved responder status in the 12-week interval compared with 17.1% in the placebo group (6.8% and 8.0% differences in the 75 mg eluxadoline group and the 100 mg eluxadoline group versus placebo, respectively), with the differences between groups being statistically significant. No calculation of confidence interval was available. For the same 12-week interval in IBS-3002, there was a higher percentage of responders in the eluxadoline groups: 28.9% in the 75 mg group, 29.6% in the 100 mg group, and 16.2% in the placebo group, also with statistically significant differences compared with placebo (12.7% and 13.4% differences in the 75 mg eluxadoline group and the 100 mg eluxadoline group versus

placebo, respectively). On the time interval of one to 26 weeks, in IBS-3001, 23.4% of patients in the 75 mg eluxadoline group and 29.3% in the 100 mg eluxadoline group achieved responder status compared with 19.0% responders in the placebo group (4.4% and 10.0% differences in the 75 mg eluxadoline group and the 100 mg eluxadoline group versus placebo, respectively), with the differences between the 75 mg eluxadoline group and placebo group not achieving statistical significance and the difference between the 100 mg eluxadoline group and placebo group achieving statistical significance. No calculation of confidence interval was available. For the same interval of 26-week in IBS-3002, there was a higher percentage of responders in the active eluxadoline groups; 30.4% in the 75 mg group, 32.7% in the 100 mg group, and 20.2% in the placebo group, also with statistically significant differences compared with placebo (10.2% and 12.5% differences in the 75 mg eluxadoline group and the 100 mg eluxadoline group versus placebo, respectively).

A breakdown of the primary outcome to its components was reported in the studies as secondary outcomes. The worst abdominal pain results did not show any statistically significant differences between eluxadoline groups and placebo groups in either study or the pooled results; specifically, at the 12-week interval, IBS-3001 reported 42.4% pain responders in the 75 mg eluxadoline group, 43.2% pain responders in the 100 mg eluxadoline group, and 39.6% responders in the placebo group, while IBS-3002 reported 48.0% responders in the 75 mg eluxadoline group, 51.0% responders in the 100 mg eluxadoline group, and 45.3% responders in the placebo group. During the 26-week interval, IBS-3001 reported 45.2% pain responders in the 75 mg eluxadoline group, 46.5% pain responders in the 100 mg eluxadoline group, and a 43.3% responders in the placebo group, while IBS-3002 reported 47.5% responders in the 75 mg eluxadoline group, 50.0% responders in the 100 mg eluxadoline group, and 44.8% responders in the placebo group. The stool consistency results show statistically significant differences between the eluxadoline groups and placebo at all time points and across both studies; specifically, at the 12-week interval, IBS-3001 reported 30.0% responders in the 75 mg eluxadoline group, 34.3% responders in the 100 mg eluxadoline group, and a 22.0% responders in the placebo group, while IBS-3002 reported 37.0% responders in the 75 mg eluxadoline group, 35.6% responders in the 100 mg eluxadoline group, and 20.9% responders in the placebo group. During the 26-week interval, IBS-3001 reported 28.1% responders in the 75 mg eluxadoline group, 34.0% responders in the 100 mg eluxadoline group, and a 24.1% responders in the placebo group, while IBS-3002 reported 34.4% responders in the 75 mg eluxadoline group, 39.8% responders in the 100 mg eluxadoline group, and 23.6% responders in the placebo group. The benefit as shown by the composite outcome in both trials was driven primarily by stool consistency but not worst abdominal pain. This was also suggested early in the phase II trial (see Appendix 5).

Other outcomes that are of relevance to this CDR review include bowel movement frequency, abdominal discomfort score, urgency episodes, and IBS-QoL total score responders. All of these outcomes were reported as secondary outcomes in both studies with no adjustment for multiple testing. Bowel movement frequency shows [redacted] versus placebo [redacted]. Specifically, at week 12, the risk ratios of bowel movement frequency in IBS-3001 were [redacted] in the comparisons between the 75 mg eluxadoline group and placebo, and between the 100 mg eluxadoline group and placebo, respectively. The risk ratios of bowel movement frequency in IBS-3002 at the same end point were [redacted] in the comparisons between the 75 mg eluxadoline group and placebo, and between the 100 mg

eluxadoline group and placebo, respectively. [redacted]results were observed at the 26-week end point. Abdominal discomfort scores also show a [redacted]in [redacted]. Similar results were observed in the urgency episodes.

Health-related quality of life as measured using the IBS-QoL questionnaire was analyzed in two ways: the least squares mean difference of the total score between the eluxadoline groups and the placebo groups, and the percentage of responders using the minimal clinically important difference (MCID) value of 14 points. Overall, comparisons using the least squares mean difference showed statistically significant differences between the active groups and placebo except at week 26 and week 30 in the 100 mg eluxadoline arm in IBS-3002. However, when using the MCID definition to determine responders, no statistically significant differences were found in either study except in the eluxadoline 100 mg group at week 52 in IBS-3001.

Harms

Overall, 60.5%, 55.3%, and 55.5% of patients in the eluxadoline 75 mg eluxadoline 100 mg, and placebo groups, respectively, of IBS-3001 experienced at least one adverse event. Similarly, 59.9%, 61.8%, and 55.9% of patients in the 75 mg eluxadoline, 100 mg eluxadoline, and placebo groups, respectively, of IBS-3002 experienced at least one adverse event. Constipation was the most common adverse event in the eluxadoline treatment groups, occurring in more patients than in the placebo groups. Specifically, in IBS-3001; 6.3%, 9.2% and 2.8% reported constipation in each of the 75 mg eluxadoline group, 100 mg eluxadoline group, and placebo groups, respectively. While in IBS-3002, 8.7%, 7.9%, and 2.1% experienced constipation in each of the 75 mg eluxadoline group, 100 mg eluxadoline group, and placebo groups, respectively. Nausea was another adverse event that occurred in a higher percentage of patients in the eluxadoline groups compared with placebo groups. Other adverse events occurred in a similar percentage of patients between treatment groups. Serious adverse events were recorded in 5.8%, 5.6%, and 3.7% of patients in the eluxadoline 75 mg, eluxadoline 100 mg, and placebo groups, respectively, in IBS-3001. For IBS-3002, 2.4%, 3.7%, and 2.1% of patients in the 75 mg, 100 mg, and placebo groups, respectively, experienced at least one adverse event. No single serious adverse had a frequency of greater than 1%. In IBS-3001, the withdrawals due to adverse events were reported at 8.2%, 9.6%, and 3.7% for the 75 mg, 100 mg, and the placebo groups, respectively. In IBS-3002 the withdrawals due to adverse events were reported at 8.4%, 7.4%, and 5.0% for the 75 mg, 100 mg, and the placebo groups, respectively. Constipation and abdominal pain were the two most common reasons for discontinuation. One death was reported in IBS-3001 but it was not deemed to be caused by the treatment. In IBS-3001 and IBS-3002, pancreatitis or acute pancreatitis was reported in seven patients, all of whom were in the eluxadoline treatment groups. Patients with prior cholecystectomy had higher percentages of having at least one adverse event when compared with the general study population. In IBS-3001: 73.8%, 72.5%, and 79.8% of patients with cholecystectomy experienced at least one adverse event in each of the 75 eluxadoline group, 100 eluxadoline group, and placebo group, respectively. In IBS-3002, percentages of patients with cholecystectomy were also higher than the general study population; 70.4%, 70.3%, and 73.9% of patients with cholecystectomy experienced at least one adverse event in each of the 75 eluxadoline group, 100 eluxadoline group, and placebo group, respectively.

Potential Place in Therapy[a]

First-line management of IBS-D is focused on behavioural advice, including suggested dietary changes and psychological well-being, and providing reassurance as to the benign nature of the syndrome. While medications are commonly used for symptoms of IBS-D, including antidiarrheals, tricyclic antidepressants, and antispasmotics, there is minimal evidence for their effectiveness in the short- or long-term. It is likely that the introduction of eluxadoline will initially generate some degree of excitement among prescribers and patients, hopeful that this medication represents the long-sought cure for their symptoms.

Given the mean age of onset at a relatively young age and a lack of a cure for IBS-D, there exists a large number of patients who have already tried a number of different drugs whose effects were either absent, or at best, transient, incomplete, and inconsistent. Therefore, it is likely that eluxadoline would be used by patients who have persistent or recalcitrant symptoms and who have failed multiple other drugs.

For relatively new cases of IBS-D, it is more difficult to define how this medication will be used compared with other therapies. In the cases where drug therapy is used, eluxadoline will likely be used primarily when other antidiarrheal drugs (loperamide, diphenoxylate), which are less expensive and more familiar, have failed to provide adequate relief. However, the clinical expert consulted suspects that this class of drugs will be less efficacious, as these patients have already shown a lack of responsiveness to other medications that activate opioid receptors.

For patients with IBS-D who also have a predominant component of abdominal pain, or patients where pain is the symptom most negatively affecting quality of life, it is likely that eluxadoline would be used when current therapies such as tricyclic antidepressants have failed. In patients where tricyclic antidepressants have been completely ineffective or where use is limited by side effects, eluxadoline may be used instead. It may also be used as a concurrent medication in patients with partial response.

The duration of therapy is likely to vary between patients. Given the relatively low response rates in the randomized controlled trials relative to placebo, as well as the relatively small magnitude of effect on abdominal pain specifically, eluxadoline is a medication that may have more subtle benefits in clinical practice. In clinical practice, patients with treatment-resistant symptoms are also highly likely to have concurrent mental health disease and personality traits that are strongly predictive of a lack of treatment response to any therapy. The clinical expert consulted for this review suspects that there will be a significant amount of short, circumscribed use and intermittent use, but relatively little long-term use. There is also the potential for eluxadoline to be a component of polypharmacy in the elderly and other personal care home residents, where it might be prescribed for episodic diarrhea and then never actively deprescribed.

As clinicians rarely make a positive diagnosis of IBS-D, eluxadoline is likely to be used off-label by patients who have abdominal symptoms (predominantly diarrhea symptoms) but do not meet official criteria for having IBS-D, or by patients with IBS with mixed bowel habits who are in a diarrheal phase, or for whom diarrhea is the most troubling symptom.

[a] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Conclusions

Two phase III, double-blind, randomized, placebo-controlled, parallel-group trials were included in the CDR systematic review (IBS-3001 and IBS-3002). Eluxadoline administered at 75 mg twice daily or 100 mg twice daily is statistically superior to placebo in patients with IBS-D based on the primary composite outcome of worst abdominal pain score and stool consistency responders. The benefit of eluxadoline was primarily driven by stool consistency rather than the reduction of pain. Nearly two-thirds of the patients in the eluxadoline treatment groups were non-responders as per the definition of composite primary outcome. In addition, the difference in the percentage of responders in the eluxadoline group versus placebo was approximately 10%. There is no clear benefit on patients' quality of life when measured as the percentage of patients who met the pre-specified MCID threshold. Additionally, the clinically significant benefit on other outcomes, such as urgency episodes, bowel movement frequency, and abdominal discomfort, was unclear. The most common adverse events reported were constipation and abdominal pain. A serious adverse event that was only recorded in eluxadoline-treated patients was pancreatitis or acute pancreatitis.

Table 1: Summary of Results

Outcome	IBS-3001			IBS-3002			Pooled Efficacy Results		
	Eluxadoline 75 mg b.i.d. N = 427	Eluxadoline 100 mg b.i.d. N = 426	Placebo b.i.d. N = 427	Eluxadoline 75 mg b.i.d. N = 381	Eluxadoline 100 mg b.i.d. N = 382	Placebo b.i.d. N = 382	Eluxadoline 75 mg b.i.d. N = 808	Eluxadoline 100 mg b.i.d. N = 806	Placebo b.i.d. N = 809
Pain responders, ITT population, 1 to 12 weeks interval									
n (%)	181 (42.4)	184 (43.2)	169 (39.6)	183 (48.0)	195 (51.0)	173 (45.3)	364 (45.0)	377 (46.8)	342 (42.3)
P value	0.404	0.284	–	0.448	0.111	–	0.261	0.069	
Difference versus placebo, % (95% CI)[a]	NR	NR	NR	NR	NR	NR	2.7 (NR)	4.5 (NR)	–
Pain responders, ITT population, 1 to 26 weeks interval									
n (%)	193 (45.2)	198 (46.5)	185 (43.3)	181 (47.5)	191 (50.0)	171 (44.8)	374 (46.3)	389 (48.3)	356 (44.0)
P value	0.582	0.355	–	0.448	0.148	–	0.357	0.086	–
Difference versus placebo, % (95% CI)[a]	NR	NR	NR	NR	NR	NR	2.3 (NR)	4.3 (NR)	–
Stool consistency responders, ITT population, 1 to 12 weeks interval									
n (%)	128 (30.0)	146 (34.3)	94 (22.0)	141 (37.0)	136 (35.6)	80 (20.9)	269 (33.3)	280 (34.7)	174 (21.5)
P value	**0.008**	**< 0.001**	–	**< 0.001**	**< 0.001**	–	**< 0.001**	**< 0.001**	–
Difference versus placebo, % (95% CI)[a]	NR	NR	NR	NR	NR	NR	11.8 (NR)	13.2 (NR)	–
Stool consistency responders, ITT population, 1 to 26 weeks interval									
n (%)	120 (28.1)	145 (34.0)	103 (24.1)	131 (34.4)	152 (39.8)	90 (23.6)	251 (31.1)	297 (36.8)	193 (23.9)
P value	0.186	**0.001**	–	**< 0.001**	**< 0.001**	–	**0.001**	**0.001**	–
Difference versus placebo, % (95% CI)[a]	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	7.2 (NR)	12.9 (NR)	–
Composite responders (pain and stool consistency), ITT population (IBS-3001 and IBS-3002 primary outcome), 1 to 12 weeks interval (FDA primary end point)									
n (%)	102 (23.9)	107 (25.1)	73 (17.1)	110 (28.9)	113 (29.6)	62 (16.2)	NR (26.2)	NR (27.0)	NR (16.7)
P value	0.014	0.004	–	< 0.001	< 0.001	–	< 0.001	< 0.001	–
Difference versus placebo, % (95% CI)[a]	6.8 (NR)	8.0 (NR)	–	12.7 (NR)	13.4 (NR)	–	9.5 (NR)	10.3 (NR)	–
Composite responders (pain and stool consistency), ITT population (IBS-3001 and IBS-3002 primary outcome), 1 to 26 weeks interval (EMA primary end point)									
n (%)	100 (23.4)	125 (29.3)	81 (19.0)	116 (30.4)	125 (32.7)	77 (20.2)	NR (26.7)	NR (31.0)	NR (19.5)

Outcome	IBS-3001			IBS-3002			Pooled Efficacy Results		
P value	0.112	**< 0.001**	–	**0.001**	**< 0.001**	–	**< 0.001**	**< 0.001**	–
Difference versus placebo, % (95% CI)[a]	4.4 (NR)	10.3 (NR)	–	10.2 (NR)	12.5 (NR)	–	7.2 (NR)	11.5 (NR)	–
Bowel frequency, ITT population, at 12 weeks									
Risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Eluxadoline 75 mg b.i.d. N = 427	**Eluxadoline 100 mg b.i.d. N = 426**	**Placebo b.i.d. N = 427**	**Eluxadoline 75 mg b.i.d. N = 381**	**Eluxadoline 100 mg b.i.d. N = 382**	**Placebo b.i.d. N = 382**	**Eluxadoline 75 mg b.i.d. N = 808**	**Eluxadoline 100 mg b.i.d. N = 806**	**Placebo b.i.d. N = 809**
Risk ratio (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bowel frequency, ITT population, at 26 weeks									
Risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risk ratio (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal discomfort score, ITT population, at 12 weeks									
Least squares mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal discomfort score, ITT population, at 26 weeks									
Least squares mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urgency episodes, ITT population, at 12 weeks									
Risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risk ratio (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IBS-QoL total score responder, ITT population, at 12 weeks									
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus placebo, % (95% CI)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IBS-QoL total score responder, ITT population, at 26 weeks									
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Outcome	IBS-3001			IBS-3002			Pooled Efficacy Results		
			[redacted]			[redacted]			
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus placebo, % (95% CI)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IBS-QoL total score responder, ITT population, at 52 weeks									
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus placebo, % (95% CI)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Harms outcomes, safety population									
	Eluxadoline 75 mg b.i.d. N = 428	**Eluxadoline 100 mg b.i.d. N = 479**	**Placebo b.i.d. N = 427**	**Eluxadoline 75 mg b.i.d. N = 379**	**Eluxadoline 100 mg b.i.d. N = 380**	**Placebo b.i.d. N = 381**	NR	NR	NR
SAEs									
Patients with > 0 SAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most common SAEs	No SAE with frequency > 1%								
WDAEs									
WDAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most common reasons									
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NOTABLE HARMS									
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b.i.d. = twice daily; CI = confidence interval; EMA = European Medicines Agency; IBS=QoL = Irritable Bowel Syndrome Quality of Life questionnaire; ITT = intention to treat; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Note: Bold *P* value indicates statistical significance.

[a] Difference versus placebo was calculated by Health Canada reviewer in the Health Canada Reviewer's Report.

Introduction

Disease Prevalence and Incidence

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder associated with changes in the stool consistency, bowel habits, and with symptoms of abdominal discomfort/pain and bloating.[1] Based on the predominant stool consistency, the diagnosis of IBS can be sub-grouped into IBS with predominant diarrhea (IBS-D), IBS with predominant constipation (IBS-C), or IBS with mixed bowel habits (IBS-M).[1] IBS-D is mainly characterized by the passage of loose stool. Also commonly present is an abnormal frequency of defecation (more than two bowel movements per day).[2] The patient group input received for this review indicates that patients living with IBS-D suffer socially and lose independence as they are consistently aware of the potential need to use a washroom. Chronic diarrhea causes patients to miss school, work, and social opportunities, and greatly limits daily activities. The diagnosis of IBS is based on the exclusion of certain organic diseases and the presence of symptoms as described in Rome diagnostic criteria. The most recent update to the Rome criteria (Rome IV) established the following diagnostic criteria:

- "Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria:
    1. Related to defecation
    2. Associated with a change in frequency of stool
    3. Associated with a change in form (appearance) of stool
- Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis."[1]

Rome III criteria specified pain or discomfort rather than just pain as outlined in the new Rome IV criteria. Also, according to Rome III criteria, patients should have had pain or discomfort in at least three days per month in the last three months, as opposed to at least one day per week in the last three months, as outlined in the Rome IV criteria.[3] It is argued that the new criteria decreases the prevalence of patients that would be diagnosed with IBS-D, and that only patients who have more prominent pain symptoms would fit under the new criteria.[4]

A recent survey of 2,961 respondents from Canada, using the Rome IV diagnosis criteria, reported an estimated prevalence of 5.7% of IBS patients in Canada.[5] The same survey indicates that approximately 35% of patients identified as having the IBS-D subtype, 41% as having the IBS-M, and 18% as having IBS-C, with 6% not sure about their subtype.[5] Previous Canadian studies using other diagnostic criteria (Rome I to III, Manning, self-reporting) have reported the prevalence of IBS-D to vary between 2.4% to 25.2%.[6] No published literature was identified that assessed the incidence of IBS in Canada. However, one extrapolation of a French study using the Rome II criteria calculated that approximately 120,000 Canadians are diagnosed with IBS each year.[6]

Standards of Therapy

Once a diagnosis of IBS-D is made, the overall aims of treatment are to address the symptoms and increase the overall quality of life for the patient. In Canada, there are no standard treatment guidelines regarding treatment management. However, lifestyle and dietary changes are considered for all patients. For patients with IBS-D, these would include reduction of caffeine, indigestible carbohydrates, and lactose intake.[7] Other non-pharmacological management options include a step-wise approach in excluding potential food triggers and the addition of probiotics.

Pharmacological treatments for patients with IBS-D mainly include antidiarrhea, antidepressant, and antispasmodic medications. Many of these medications are considered off-label uses for treatment of IBS-D as there are no Health Canada–approved pharmacological drugs indicated specifically for the treatment of IBS-D. Antidiarrhea medication would include opioid drugs such as loperamide; bile acid sequestrants such as cholestyramine and colesevelam are other examples of antidiarrhea drugs used in IBS-D.[8-10] Antispasmodics, which aim to address pain symptoms associated with IBS, include pinaverium, hyoscine, otilonium, cimetropium, and dicyclomine.[11,12]

Feedback reported from patient group input to CADTH Common Drug Review (CDR) indicated the need for additional treatment options, as some patients cannot find a workable treatment plan with the options that exist, while others find themselves depleting their options as they try several different approaches. On the other hand, some patients find a treatment option that works for them. Because the exact etiology of IBS remains largely unknown, patients desire access to as many options as possible to meet their individual needs.

Drug

Eluxadoline (Viberzi) is a mixed mu opioid receptor agonist and delta opioid receptor antagonist indicated for the treatment of IBS-D in adult patients. Eluxadoline is given orally at a dose of 100 mg, twice daily. A reduced dose of 75 mg is recommended for geriatric patients or patients who cannot tolerate the 100 mg dose. Rare but serious adverse events reported in the product monograph are sphincter of Oddi spasms and pancreatitis.

While there are no available approved comparators to eluxadoline, the drug aims to reduce pain and improve stool consistency. Loperamide is commonly used off-label to address stool consistency and frequency aspects of IBS-D, while tricyclic antidepressants are commonly used off-label to alleviate pain associated with IBS.

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of eluxadoline for the treatment of IBS-D in adults.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to CDR and Health Canada, as well as those meeting the selection criteria presented in Table 2.

Table 2: Inclusion Criteria for the Systematic Review

Patient Population	Adults ≥ 18 years with a diagnosis of IBS-D Subgroups: • treatment experience with opioids used off-label for IBS-D (e.g., loperamide, diphenoxylate with atropine [Lomotil]) • sex • presence of comorbid mood disorder
Intervention	Eluxadoline 75 mg to 100 mg twice daily
Comparators	Off-label drugs:[a] • opioids (e.g., loperamide, diphenoxylate with atropine [Lomotil]) • bile acid sequestrants (e.g., cholestyramine) • antispasmodics (e.g., pinaverium bromide, hyoscine butylbromide) • specifically for relief of abdominal pain in IBS: • TCAs (e.g., amitriptyline, desipramine) Placebo
Outcomes	**Key efficacy outcomes:** • stool consistency • abdominal pain intensity • stool frequency **Other efficacy outcomes:** • relief of IBS symptoms: o abdominal discomfort o urgency o unpredictability • ADL[b] • HRQoL[b] **Harms outcomes:** • mortality • AEs • WDAEs • AEs (pancreatitis; abuse potential, adverse events in patients with a history of cholecystectomy)

Study Design	Published and unpublished phase III RCTs

ADL = activities of daily living; AE = adverse event; HRQoL = health-related quality of life; IBS = Irritable bowel syndrome; IBS-D = Irritable bowel syndrome with diarrhea; RCT = randomized controlled trial; SAE = serious adverse event; TCA = tricyclic antidepressant; WDAE = withdrawal due to adverse event.
[a] Off-label drugs do not have a specific Health Canada indication for the treatment of IBS-D. However the clinical expert consulted for this review confirmed their common off-label use in IBS-D in Canada. In addition, their use is supported by clinical guidance documents from National Institute for Health and Care Excellence and the American Gastroenterological Association.[8,13]
[b] Outcomes identified as important to patients in the patient group input submitted to CADTH Common Drug Review.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Viberzi (and synonyms).

No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on March 27, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on July 18, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 2; excluded studies (with reasons) are presented in Appendix 3.

Results

Findings from the Literature

A total of 2 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 3 and described in the included studies section. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

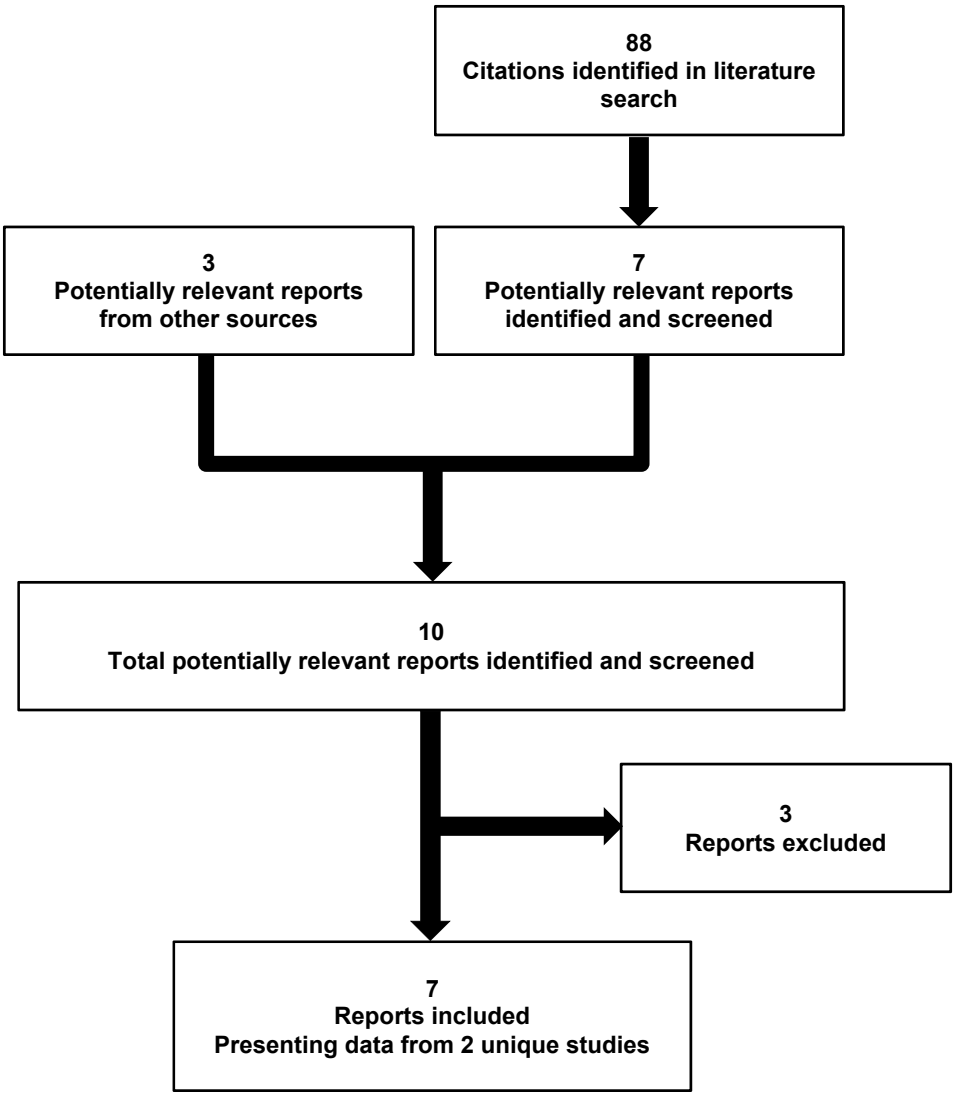

Table 3: Details of Included Studies

		IBS-3001	IBS-3002
Designs and Populations	**Study Design**	Randomized, double-blind, placebo-controlled, phase III	
	Locations	Canada, UK, US	
	Randomized (N)	1,281	1,146
	Inclusion Criteria	• Adult patients between 18 to 80 years of age. • Patients diagnosed with Irritable bowel syndrome (IBS), with a subtype of diarrhea as defined by the Rome III criteria. • Patients had a colonoscopy performed: o Within 10 years prior to prescreening if patient is at least 50 years of age (sigmoidoscopy, double-contrast barium enema, or CT colonography within the past 5 years is acceptable). o At any age since the onset of: weight loss within the past 6 months, nocturnal symptoms, familial history of first-degree relatives with colon cancer, or blood mixed with stool (excluding hemorrhoids). • Patient had an average of worst abdominal pain scores in the past 24 hours of > 3.0 on a 0 to 10 scale over the week before randomization. • Patient had an average BSS consistency score of ≥ 5.5 and at least 5 days with a BSS score ≥ 5 on a 1 to 7 scale over the week before randomization. • Patient had an average daily IBS-D global symptom score of ≥ 2.0 on a 0 to 4 scale (0 corresponds to no symptoms and 4 corresponds to very severe symptoms) over the week before randomization. • Female patients must be: postmenopausal, surgically sterile, or abstinent, or practising an effective method of birth control.	
	Exclusion Criteria	• Patient diagnosed with IBS with a subtype of constipation, mixed, or unsubtyped IBS by the Rome III criteria. • History of inflammatory or immune-mediated GI disorders including inflammatory bowel disease (i.e., Crohn's disease, ulcerative colitis) and celiac disease. • History of diverticulitis within 3 months prior to prescreening. • History of intestinal obstruction, sphincter of Oddi dysfunction, stricture, toxic megacolon, GI perforation, fecal impaction, gastric banding, bariatric surgery, adhesions, ischemic colitis, or impaired intestinal circulation (e.g., aortoiliac disease). • Any of the following surgical history: o Cholecystectomy with any history of postcholecystectomy biliary tract pain o Any abdominal surgery within the 3 months prior to prescreening o Major gastric, hepatic, pancreatic, or intestinal surgery. • History of substance dependency, excluding nicotine and caffeine, within 2 years prior to prescreening. [redacted]	
Drugs	**Intervention**	• 75 mg eluxadoline, oral, twice daily • 100 mg eluxadoline, oral, twice daily	
	Comparator(s)	• Placebo	

		IBS-3001	IBS-3002
Duration	Run-in	4-week (1 week prescreening, and 3 weeks screening)	4-week (1 week prescreening, and 3 weeks screening)
	Double-blind	52-week	26-week
	Follow-up	2-week	4-week (single-blinded withdrawal assessment period)
Outcomes	**Primary End Point**	• Composite responder percentage at 12 or 26 weeks defined as at least 50% of days, during the interval of interest, where: o Daily pain response: worst abdominal pain scores in the past 24 hours improved by ≥ 30% compared with baseline AND o Daily stool consistency response: BSS score < 5 or the absence of a bowel movement if accompanied by ≥ 30% improvement in worst abdominal pain compared with baseline pain.	
	Other End Points	• Pain responders: meeting the daily pain response criteria for at least 50% of days • Stool consistency: meeting the daily stool consistency response criteria for at least 50% of days during the interval of interest • IBS-D global symptom responders: meeting the daily IBS-D global symptom response criteria (IBS-D global symptom score of 0 [none] or 1 [mild]; or a daily IBS-D global symptom score improved by ≥ 2.0 compared with the baseline average) for at least 50% of days • IBS-QoL responders: achieving at least a 14-point improvement in IBS-QoL total score from baseline to the applicable visit • IBS-AR responders: defined as those patients with a weekly response of "Yes" to adequate relief of their IBS symptoms for at least 50% of the total weeks during the interval of interest • Discomfort: changes from baseline in daily abdominal discomfort scores • Bloating: changes from baseline in daily abdominal bloating scores • Frequency: number of bowel movements per day • Incontinence: number of bowel incontinence episodes per day and number of incontinence-free days • Urgency: number of urgency episodes per day	
Notes	**Publications**	• Lembo et al. (2016)[14] • Lacy et al. (2017)[15] • Cash et al. (2017)[16] • Chey et al. (2017)[17]	

CT = computed tomography; BSS = Bristol stool scale; GI = gastrointestinal; IBS = Irritable bowel syndrome; IBS-AR = adequate relief of Irritable bowel syndrome symptoms; IBS-D = Irritable bowel syndrome with diarrhea; IBS-QoL = Irritable Bowel Syndrome Quality of Life questionnaire.

Note: Three additional reports were included.[13,18,19]

Source: IBS-3001 and IBS-3002 clinical study reports.[20,21]

Included Studies

Description of Studies

The CDR systematic search of the literature identified two studies for inclusion. IBS-3001 and IBS-3002 were phase III, double-blind, randomized, placebo-controlled, parallel-group, superiority studies. IBS-D patients were randomized (IBS-3001, N = 1,281; and IBS-3002, N = 1,146) to receive 75 mg twice-daily eluxadoline, 100 mg twice-daily eluxadoline, and placebo groups in a 1:1:1 ratio, stratified by region. The studies' primary outcome was a composite of pain and stool consistency responders at 12 weeks (FDA end point requirement) or 26 weeks (European Medicines Agency [EMA] end point requirement). Both studies were identical in design except that IBS-3001 included an additional 26 weeks of double-blind treatment with a subsequent two weeks of no treatment follow-up, while IBS-3002 included an additional four weeks of a single-blinded withdrawal assessment period. Both studies were conducted in Canada, the UK, and US.

Populations

Inclusion and Exclusion Criteria

Eligible patients were adults diagnosed with IBS-D as defined by the Rome III criteria (both studies were initiated prior to the publication of Rome IV criteria). Patients had to have had a colonoscopy if they were over the age of 50 or if they displayed any "alarm features" that may indicate organic causes of the exhibited symptoms. Eligible patients had to demonstrate a moderate to high score of worst abdominal pain (WAP), stool consistency on the Bristol stool scale (BSS: a standardized method for the classification of stool form, which is a proxy for determining stool consistency, based on an ordinal scale from type 1 [hardest] to type 7 [softest], with types 1 and 2 considered abnormally hard and indicative of constipation, and types 6 and 7 being abnormally loose/liquid stools indicative of diarrhea), and the IBS-D global symptom score (a 0-to-4 scale where 0 corresponds to no symptoms and 4 corresponds to very severe symptoms). Exclusion criteria aimed to exclude patients with potential bowel-related comorbidities or recent use of drugs that may affect patient response to eluxadoline. In addition, the exclusion criteria aimed to exclude patients with a potential susceptibility to drug addiction.

Baseline Characteristics

Baseline demographics were generally similar between treatment groups and between the two studies. The placebo group in IBS-3002 had an older mean age than the treatment groups (47.1 years of age compared with 45.0 and 45.7 in the 75 mg and 100 mg eluxadoline groups, respectively). Also, IBS-3002 had a lower mean number of incontinence episodes than IBS-3001 — a total mean of 0.96 (standard deviation [SD] 1.63) — across all groups in IBS-3002 and a total mean of 1.37 (SD 2.02) across all groups in IBS-3001. In both studies, the majority of the participants were female (approximately 66%) and white (approximately 86%) and that patients 65 years of age or older constituted only 9% of the studies' population. Table 4 provides a summary of patients' baseline characteristics.

Table 4: Summary of Baseline Characteristics

Characteristics	IBS-3001 (Enrolled Set)			IBS-3002 (Enrolled Set)		
	Eluxadoline 75 mg b.i.d. N = 429	Eluxadoline 100 mg b.i.d. N = 426	Placebo b.i.d. N = 427	Eluxadoline 75 mg b.i.d. N = 381	Eluxadoline 100 mg b.i.d. N = 383	Placebo b.i.d. N = 382
Age, mean years (SD)	44.5 (13.2)	44.4 (13.9)	45.8 (14.1)	45.0(13.27)	45.7(13.3)	47.1 (13.8)
Gender, n (%)						
Male	151 (35.2)	143 (33.6)	150 (35.1)	120 (31.5)	126 (32.9)	132 (34.6)
Female	278 (64.8)	283 (66.4)	277 (64.9)	261 (68.5)	257 (67.1)	250 (65.4)
Race, n (%)						
White	374 (87.2)	368 (86.4)	370 (86.7)	327 (85.8)	318 (83.0)	329 (86.1)
Black	46 (10.7)	48 (11.3)	46 (10.8)	46(12.1)	51 (13.3)	43 (11.3)
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristics	IBS-3001 (Enrolled Set)			IBS-3002 (Enrolled Set)		
	Eluxadoline 75 mg b.i.d. N = 429	Eluxadoline 100 mg b.i.d. N = 426	Placebo b.i.d. N = 427	Eluxadoline 75 mg b.i.d. N = 381	Eluxadoline 100 mg b.i.d. N = 383	Placebo b.i.d. N = 382
BMI (kg/m^2)						
Mean (SD)	30.7 (7.4)	31.2 (7.9)	30.63 (7.2)	30.79 (8.2)	30.45 (7.7)	29.79 (6.9)
Worst abdominal pain score						
Mean (SD)	6.1 (1.5)	6.2 (1.5)	6.2(1.6)	6.0 (1.5)	6.0(1.5)	6.0 (1.5)
Abdominal bloating[a]						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	5.9 (2.00)	5.8 (2.1)	6.1(2.0)	5.7 (2.0)	5.6 (2.0)	5.70 (2.1)
Abdominal discomfort score						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stool consistency score (BSS)						
Mean (SD)	6.2 (0.4)	6.38 (0.4)	6.3 (0.4)	6.2 (0.4)	6.2 (0.4)	6.2 (0.4)
Daily bowel movement frequency						
Mean (SD)	4.8 (2.7)	5.0 (3.0)	5.0 (2.7)	4.7 (2.3)	4.9 (4.2)	4.7 (2.2)
Urgency episodes						
Mean (SD)	3.5 (2.2)	3.5 (2.1)	3.7 (2.7)	3.4 (2.2)	3.6 (4.1)	3.4 (2.0)
Daily incontinence episodes						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incontinence-free days						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IBS-D global symptoms score						
Mean (SD)	2.8 (0.55)	2.9 (0.5)	2.9 (0.5)	2.8 (0.5)	2.8 (0.5)	2.8 (0.5)

b.i.d. = twice daily; BMI = body mass index; BSS = Bristol stool scale; IBS-D = Irritable bowel syndrome with diarrhea; SD = standard deviation.

[a] The abdominal bloating questionnaire was not available in Spanish.

Source: IBS-3001 and 3002 Clinical Study Reports.[20,21]

In both studies the following medications were not allowed:

[redacted]

The use of at least one concomitant medication after randomization was present in [redacted] of patients in IBS-3001 and IBS-3002, across all groups, respectively.

Table 5 summarizes the percentages of the most commonly used concomitant medications across by treatment groups in both studies.

Table 5: Most Commonly Used (> 5%) Concomitant Medication After Randomization

Concomitant Medication	3001 (Enrolled Set)			3002 (Enrolled Set)		
	Eluxadoline 75 mg b.i.d. N = 429	Eluxadoline 100 mg b.i.d. N = 426	Placebo b.i.d. N =427	Eluxadoline 75 mg b.i.d. N = 381	Eluxadoline 100 mg b.i.d. N = 383	Placebo b.i.d. N = 382
[redacted]						

b.i.d. = twice daily.

Source: IBS-3001 and 3002 Clinical Study Reports.[20,21]

Interventions

Patients were randomized into three groups: the 75 mg eluxadoline treatment group received 75 mg eluxadoline pills twice daily, the 100 mg eluxadoline treatment group received 100 mg eluxadoline pills twice daily, and the placebo group received matching placebo pills twice daily. Patients were instructed to take the allocated pills during the morning and the evening with food and to be swallowed with liquid.

Rescue medication in the form of loperamide for uncontrolled diarrhea was allowed after the screening period at 2 mg every six hours to a maximum of 8 mg/day, 14 mg over two days continuous, or 22 mg over seven days continuous. No other rescue medication was allowed.

Outcomes

Composite Responder (Primary Clinical Outcome)

The primary clinical outcome was a composite responder percentage at 12 or 26 weeks defined as at least 50% of days, during the interval of interest, where:

- daily pain response: WAP scores in the past 24 hours improved by ≥ 30% compared with baseline

and

- daily stool consistency response: BSS score less than 5 or the absence of a bowel movement if accompanied by ≥ 30% improvement in WAP compared with baseline pain.

Patients were provided with electronic diaries and were requested to update them daily. Patients were classified as either a responder or nonresponder based on achieving the aforementioned conditions. Patients had to have made at least 60 days of diary entries over the 12-week interval and at least 110 days of diary entries over the 26-week interval to be considered a responder. Patients with fewer than the necessary number of diary entries were automatically assigned a nonresponder status. No validation or a measure of minimal important clinical difference (MCID) is available for the primary outcome.

Pain Responders (Secondary Outcome)

A pain responder is a patient who recorded in the diary that a WAP score in the past 24 hours improved by 30% or more compared with baseline, on at least half the days over a 12-week or a 26-week interval. The WAP score is a patient-reported outcome, based on an 11-point ordinal scale from 0 to 10, with 0 representing no pain and 10 representing the worst imaginable pain.[20,21] The 11-point scale is used to evaluate a patient's "worst abdominal pain" experienced in the previous 24 hours based on patient recall.[20,21] No evidence of validity was identified for the WAP score, although it has been recommended as a co-primary end point in clinical trials for IBS, as it is a measure of one of the two major symptoms of IBS, abdominal pain.[19,22,23] In addition, no measure of an MCID was found.

Stool Consistency Responders (Secondary Outcome)

A stool consistency responder is a patient who recorded, on at least half the days over a 12-week or a 26-week interval, a daily stool consistency score of less than 5 using the BSS tool or recorded an absence of bowel movements when accompanied by WAP of 30% or less compared with baseline. The BSS, also known as the Bristol Stool Form Scale, is based on an ordinal scale from type 1 (hardest) to type 7 (softest), with types 1 and 2 considered abnormally hard and indicative of constipation, and types 6 and 7 being abnormally loose/liquid stools indicative of diarrhea (Table 2).[24] The BSS is a validated tool with fair patient-physician inter-rater agreement and moderate correlation with a stool's measured water content. No measure of responsiveness or MCID was found for BSS, as such, by extension, for the stool consistency responder outcome.

Irritable Bowel Syndrome with Predominant Diarrhea Global Symptom Responders (Secondary Outcome)

An IBS-D global symptom responder is a patient who recorded, on at least half the days over a 12-week or a 26-week interval, an IBS-D global symptom score of 0 or 1, or had a daily IBS-D global symptom score improved by two or more points compared with baseline average. The IBS-D global symptom score is a measurement of overall symptoms associated with IBS-D. It is a patient-reported outcome based on the previous 24 hours and is assessed on a scale from 0 to 4, where 0 corresponds to no symptoms, and 4 corresponds to very severe symptoms.[20,21] No evidence regarding the validity of the IBS-D global symptom score or measurement for MCID was identified.

Irritable Bowel Syndrome Quality of Life Responders (Secondary Outcome)

An Irritable Bowel Syndrome Quality of Life questionnaire (IBS-QoL) responder is a patient who achieved at least 14-point improvement in total score from baseline to the recorded visit (12 or 26 weeks) on at least half the days over a 12-week or a 26-week interval, an IBS-D global symptom score of 0 or 1, or had their daily IBS-D global symptom score improved by two or more points compared with baseline average. The IBS-D global symptom score is a measurement of overall symptoms associated with IBS-D. IBS-QoL consists of 34 questions that are answered by patients according to a five-point Likert scale, with 1 corresponding to having the least impact on quality of life (QoL), and five as having the greatest impact. IBS-QoL is a tool developed to capture quality of life in IBS patients in general and not specifically the IBS-D subpopulation. IBS-QoL is a validated instrument with an established MCID of 14 points.

Adequate Response of Irritable Bowel Syndrome Symptoms Responders (Secondary Outcome)

An IBS-D adequate relief responder is a patient who recorded a weekly response of "Yes" to adequate relief of their IBS symptoms for at least half of the total weeks during the 12- or 26-week intervals, had an IBS-D global symptom score of 0 or 1, or had their daily IBS-D global symptom score improved by two or more points compared with baseline average. The adequate relief of IBS symptoms (IBS-AR) end point is a patient-reported, dichotomous, single-item outcome.[20,21] It is used to assess whether a patient has experienced adequate relief of their IBS symptoms using the answer to "Over the past week, have you had adequate relief of your IBS symptoms?"[14,20,21] There was no evidence of validity identified for the IBS-AR, or an established MCID.

Discomfort Score (Other Secondary Outcome)

This was represented as changes from baseline in the daily abdominal discomfort scores. The abdominal discomfort score is a patient-reported assessment of abdominal discomfort based on 24-hour recall. It is rated on an ordinal scale from 0 to 10, with a higher score corresponding to more severe abdominal discomfort and 10 being the worst imaginable discomfort.[20,21] There was no evidence of validity identified, nor an established MCID.

Incontinence (Other Secondary Outcome)

Incontinence was represented as a patient-reported number of bowel incontinence episodes per day and as the number of incontinence-free days.

Urgency (Other Secondary Outcome)

Urgency was represented as a patient-reported number of a number of urgency episodes per day.

Frequency (Other Secondary Outcome)

Frequency was represented as a patient-reported number of bowel movements per day.

Harms-Related Outcomes

Mortality, serious adverse events, overall adverse events, and adverse events of special clinical interest (e.g., pancreatitis) were also reported. IBS-3002 administered the Subjective Opiate Withdrawal Scale (SOWS) tool to patients who completed the double-blind treatment period and entered the single-blind four-week withdrawal phase. The SOWS is a questionnaire with 16 symptoms, each having a possible score of 0 to 4, with higher scores indicative of withdrawal. Similarly, IBS-3001 administered the SOWS questionnaire but without the single-blinded withdrawal period of IBS-3002.

Statistical Analysis

Overall, both studies were designed for superiority testing on the composite end point, with an alternative hypothesis that eluxadoline is superior to placebo.

Sample Size Calculation

The sample size was determined from the assumption that the percentage of placebo responders for the primary efficacy end point will be 14% and a 10% treatment difference over placebo for any active comparator. No reference was available to indicate the evidence supporting these assumptions; it is likely that the manufacturer drew these assumptions from the phase II trial, as evident by pointing out that the number of potential drop-outs was based on the number drop-outs in the phase II trial. According to these assumptions, a sample size of 375 patients per group would yield more than 90% power for a two-sided Cochrane–Mantel–Haenszel at an alpha level of 0.025, which was determined as a Bonferroni adjustment for multi-group comparison. If the placebo response rate rises to 20% with a 10% treatment effect difference, then the power drops to > 80%.

Efficacy Analysis

Analysis of the primary outcome was conducted through the Cochrane–Mantel–Haenszel test using the intention-to-treat (ITT) analysis set. Similarly, pain responders, stool consistency responders, IBS-AR responders, and IBS-QoL responders were all analyzed through the Cochrane–Mantel–Haenszel test using the ITT analysis set. Also, a longitudinal generalized linear model was used as an exploratory analysis on the previously mentioned outcomes (composite primary outcome, pain responders, stool consistency responders, IBS-AR responders, and IBS-QoL) in addition to assessing discomfort score, urgency, and frequency using a generalized linear model.

Subgroups and Sensitivity Analyses

In its protocol analysis, the manufacturer outlined subgroups based on region, gender, and age for the composite primary outcome (12-week interval), abdominal pain (12-week interval), stool consistency (12-week interval), and IBS-D global symptoms (26-week interval). Sensitivity analyses for worst-case scenarios (in which missing data were included, and patients had to be a responder on 42 of 84 days for the 12-weeks period and 91 out of 182 days for the 26-weeks period regardless of diary compliance, with missing entries resulting in a nonresponder status for that day) that applied a two-week definition for responding as opposed to daily, and used a subset of patients with no dose interruption, were similar to the base case. Several post hoc subgroups and sensitivity analyses were also subsequently reported in regulatory reviews and published literature, including a subgroup analysis of response in patients with prior exposure to loperamide.

Missing Data

The manufacturer did not conduct any procedure to account for missing data as such measures are built into the method of collecting and reporting the outcome. Specifically, patients had to have at least 60 or 110 days of diary entries to be assessed for the response for the primary outcome at week 12 and 26, respectively. Patients who failed to meet these diary requirements for any reason were considered non-responders. This method is used to handle missing data in all responder-based outcomes. No clear description of the imputation method for the longitudinal generalized linear models was described.

Adjustments for Multiple Testing

Adjustment for multiple group comparison in the primary composite outcome was addressed using the Bonferroni correction. This adjustment is meant to address the issue of multiple testing based on the existence of multiple groups rather than testing over multiple intervals. No adjustment for multiple testing was conducted for any other outcome.

Analysis Populations

Four different analyses sets were defined in both the IBS-3001 and IBS-3002 studies:

- The enrolled set: all patients randomized or who received at least one dose of the study drug.
- The ITT analysis set: all patients randomly assigned to treatment.
- The modified ITT analysis set: all patients randomly assigned to treatment who received at least one dose of the study drug and who had a baseline and at least one post-randomization diary entry.
- The safety analysis set: all patients enrolled who received at least one dose of the study drug.

Patient Disposition

A total of 2,831 patients were screened for IBS-3001, of which 1,281 (45.2%) were enrolled, and a total of 2,521 patients were screened for IBS-3002, of which 1,146 (45.5%) were enrolled. One patient in IBS-3001 was enrolled but not randomized, while all patients in IBS-3002 were randomized. IBS-3001 had a higher percentage of discontinuation than IBS-3002 (40.1%, 39.4%, 37.0% in 3001 compared with 34.4%, 31.1%, and 28.5% for IBS-3002 in the 75 mg, 100 mg, and placebo groups, respectively). It is also noted that discontinuations were higher in the active groups than in placebo, particularly in the 75 mg eluxadoline group. In addition, the manufacturer reported an error in the interactive voice/Web response system that led to treatment misallocation in both studies: in IBS-3001, 58 patients who were assigned to the 75 mg group were given the 100 mg treatment kit on week 18 visit, 53 of whom took the wrong treatment and five returned the kits unused; in IBS-3002, 26 patients (12 patients in the 75 mg group, and 14 patients in the 100 mg group) continued to receive their medication during the single-blinded four-week follow-up period instead of switching to placebo. Patient disposition and the number of patients in each analysis set is summarized in Table 6.

Table 6: Patient Disposition

	3001 (Enrolled Set)			3002 (Enrolled Set)		
	Eluxadoline 75 mg b.i.d.	Eluxadoline 100 mg b.i.d.	Placebo b.i.d.	Eluxadoline 75 mg b.i.d.	Eluxadoline 100 mg b.i.d.	Placebo b.i.d.
Screened, N	2,831			2,521		
Enrolled, N (%)	1,281 (45.2%)			1,146 (45.5%)		
Randomized, N (%)	428 (99.8)	426(100.0)	427(100.0)	381 (100.0)	383 (100.0)	382 (100.0)
Attended week 12 visit, N (%)	341 (79.5)	330 (77.5)	342 (80.1)	296 (77.7)	301 (78.6)	312 (81.7)
Attended week 26 visit, N (%)	289 (67.4)	291 (68.3)	290 (67.9)	259 (68.0)	271 (70.8)	278 (72.8)
Completed study, N (%)	257 (59.9)	257 (60.3)	269 (63.0)	250 (65.6)	264 (68.9)	273 (71.5)
Discontinued study, N (%)	172 (40.1)	168 (39.4)	158 (37.0)	131 (34.4)	119 (31.1)	109 (28.5)
Voluntarily withdrew, N (%)	94 (21.9)	79 (18.5)	96 (22.5)	70 (18.4)	66 (17.2)	74 (19.4)
Adverse event or SAE, N (%)	36 (8.4)	45 (10.6)	16(3.7)	32 (8.4)	28 (7.3)	19 (5.0)
Lost to follow-up, N (%)	25 (5.8)	23 (5.4)	16 (3.7)	11 (2.9)	5 (1.3)	6 (1.6)
Physician decision, other, N (%)	11 (2.6)	14 (3.3)	16 (3.7)	10 (2.6)	8 (2.1)	7 (1.8)
Physician decision: lack efficacy, N (%)	2 (0.5)	3 (0.7)	7 (1.6)	1 (0.3)	5 (1.3)	3 (0.8)
Protocol violation, N (%)	3 (0.7)	4 (0.9)	4(0.9)	0	2 (0.5)	0
Sponsor decision, N (%)	1 (0.2)	0	3 (0.7)	7 (1.8)	5 (1.3)	0
Enrolled set, N	429	426	427	381	383	382
Randomized set, N	428	426	427	381	383	382
ITT analysis set, N	427	426	427	381	382	382
Safety analysis set, N	428	479	427	379	380	381
Modified ITT analysis set, N	422	421	424	376	376	379

b.i.d. = twice daily; ITT = intention to treat; SAE = serious adverse event.

Source: IBS-3001 and 3002 clinical study reports.[20,21]

Exposure to Study Treatments

At week 26, patients had [redacted] days of exposure to the allocated treatment across and within both studies (total mean of [redacted] in IBS-3001, and a total mean of [redacted] in IBS-3002). As the double-blind treatment period of IBS-3001 extended beyond 26 weeks until week 52, the full study exposure was a total mean [redacted] with [redacted] days of exposure across treatment groups. A summary of treatment exposure is presented in Table 7. Exposure to loperamide as a rescue medication was reported at [redacted] overall in both studies in the pooled 75 mg eluxadoline group, the pooled 100 mg eluxadoline group, and the pooled placebo group, respectively, during the one to 26 weeks interval. The mean number of loperamide units administered per week ranged from [redacted]. In IBS-3001, [redacted] of patients received rescue medication with loperamide: [redacted] in the 75 mg group, [redacted] in the 100 mg group, and [redacted] in the placebo group. Similar information for IBS-3002 was not found. Excessive use of loperamide was reported in [redacted] and [redacted] of patients in IBS-3001, and in [redacted] in IBS-3002 in each of the 75 mg, 100 mg, and placebo groups, respectively.

Table 7: Summary of the Duration of Exposure

	IBS-3001 (Safety Set)			IBS-3002 (Safety Set)		
	Eluxadoline 75 mg b.i.d.	Eluxadoline 100 mg b.i.d.	Placebo b.i.d.	Eluxadoline 75 mg b.i.d.	Eluxadoline 100 mg b.i.d.	Placebo b.i.d.
Overall duration of exposure at week 26 (days)						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall duration of exposure – full study (days)						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b.i.d. = twice daily; ITT = intention to treat; SD = standard deviation.

Source: IBS-3001 and 3002 clinical study reports.[20,21]

Critical Appraisal

Internal Validity

The included studies were double-blind, multi-centre, randomized, placebo-controlled superiority studies. Power analysis was reported to be conducted appropriately with reasonable assumptions of treatment effect. The study was powered to detect a difference in the primary composite outcome, and as such, a lack of statistically significant differences in other outcomes may not indicate a true lack of difference. Randomization and treatment allocation were well described and performed appropriately; patients were randomized on a 1:1:1 basis with stratification for geographic region and treatment allocation was conducted through an interactive voice/Web response system. Matching placebo was used to ensure blinding. The outcomes were patient-reported as patients were instructed to fill in electronic diaries that were used to determine the efficacy of the treatment. The duration of treatment was in line with regulatory request and the Rome Foundation (issuer of the Rome criteria) recommendation for trials conducted on patients with functional gastrointestinal conditions. In addition, IBS-3001 had an extended double-blind follow-up period of 26 weeks beyond the primary end point.

A high percentage of patients discontinuing the study was observed in both studies (40.1%, 39.4%, and 37.0% in IBS-3001 and 34.4%, 31.1%, and 28.5% for IBS-3002 in the 75 mg, 100 mg, and placebo groups, respectively), with discontinuation percentages in the eluxadoline groups higher than in the placebo groups. As several factors can affect treatment outcome, including the chronic nature of the disease, the symptomatic management aim of eluxadoline, and the use of patient-reported outcomes, it is unclear what effect this imbalance might have on the results, if any. Furthermore, the manufacturer did not use a data imputation method as a nonresponder status was automatically assigned to patients whose number of diary entries fell below a certain threshold. Specifically, patients had to have at least 60 or 110 days of diary entries to be assessed for the response for the primary outcome at week 12 and 26, respectively. Patients who failed to meet these diary requirements for whatever reason were automatically considered non-responders. The manufacturer provided several sensitivity analyses in support of this approach under a worst-case scenario and varying definitions of response.

The manufacturer reported the occurrence of [redacted] in both studies. In IBS-3001, [redacted] patients from the [redacted], [redacted] of whom [redacted]; in IBS-3002, [redacted] patients ([redacted] patients in the 75 mg group, and [redacted] patients in the 100 mg group) continued to [redacted] The manufacturer conducted [redacted]. The use of rescue medication was reported to be [redacted] in terms of loperamide units dispensed. However, information from IBS-3001 suggests that approximately [redacted] of patients [redacted] during the double-blind period. The manufacturer provided a [redacted].

The primary outcome in both studies was a composite of pain and stool consistency (using the BSS) responders. Although the BSS is a validated tool (from the perspectives of construct validity, inter-rater agreement, and correlation), no published MCID, measure of reliability, or measure of responsiveness was found. Similarly, no validation of the score for WAP, an MCID, reliability, or responsiveness was found. The lack of a responsiveness measure reduces the ability to attribute changes (or lack of changes) in the outcome to the intervention; as such it may affect the ability of the composite primary outcome to assess the true treatment effect.

Although both studies included an adjustment for multiple testing of the primary outcome using the Bonferroni method, this adjustment only addressed the multiple testing of two active groups being compared with placebo and did not address the multiple testing at different time points of the primary outcome (12-week and 26-week intervals), or any secondary outcomes. The manufacturer conducted the assessment of the primary outcome at 12 weeks for FDA regulatory requirements and 26 weeks for EMA regulatory requirements. If the results of both of these analyses are interpreted together, one of the time points would not be controlled for multiple statistical testing and should be interpreted with that in mind. In addition, the lack of adjustment for multiple testing on other outcomes such as urgency episodes, abdominal discomfort scores, and bowel movement frequency, which showed statistical significance at 0.05, may suffer from inflated type I error.

One available and relevant subgroup analysis was conducted on patients who reported loperamide use in the year prior to enrolling in the trial. It was stratified by patients who reported adequate symptom control with loperamide use and those that reported no adequate symptom control with loperamide use. The results of this subgroup analysis are considered exploratory. This subgroup analysis was a post hoc analysis and not pre-specified in the protocol section of the submitted clinical study reports of either studies. In addition, identification of patients and stratification based on potential recall of symptom control in the past years are susceptible to recall bias. Moreover, the subgroup analysis, with further stratification, is no longer considered representative of a randomized population and no baseline characteristics were reported to allow assessment of potential imbalances between treatment arms.

External Validity

No direct or indirect comparisons between eluxadoline and any commonly used pharmacological drugs in the treatment of IBS-D were available. This represents a gap in the evidence as we are unable to determine the added clinical efficacy of eluxadoline against commonly used pharmacological drugs, such as loperamide, in the treatment of IBS-D symptoms.

Overall, the clinical expert consulted on this review identified these inclusion and exclusion criteria as appropriate. There might be a concern that the exclusion criteria excluded patients with a history of abdominal pain post-cholecystectomy, as those patients might be at higher risk of sphincter of Oddi spasms and/or pancreatitis. Considering that eluxadoline is an opioid drug that predisposes patients with a cholecystectomy to sphincter of Oddi syndrome, there might be a concern that the prevalence of this condition in the trials is lower than what can be expected in the general population. Concerns regarding generalizability are also emphasized when considering that less than half of the screened patients were eligible to enroll in these trials.

Considering that IBS is a chronic condition, and while the time points of the primary outcome where aligned with the regulatory requirements, a six-month assessment may be considered short-term evidence. Although IBS-3001 did provide results at 52 weeks, the sustainability of the treatment effect beyond one year remains uncertain.

The clinical expert consulted for this review indicated that the primary outcome defined in the trials is not routinely used in clinical practice and, as such, may be of limited information value to a clinical practitioner. The clinical expert indicated that the approach to treatment is dependent on the overall patient satisfaction. Such an outcome may have been best described with a validated, properly adjusted, and specific QoL tool for IBS-D patients. As it stands, the manufacturer provided results of outcomes of adequate relief, global symptoms score, and IBS-QoL. However, the lack of validation, MCID, and adjustment for multiple outcomes in the IBS-AR and global symptoms score limits our ability to extrapolate the results of the studies' outcomes to the general IBS-D patient population. The IBS-QoL is not specific to IBS-D patients and is also not adjusted for multiple outcomes testing, greatly reducing its information value.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Table 2).

Key Efficacy Outcomes

Composite Responders (Pain and Stool Consistency)

In IBS-3001, 23.9% of patients in the 75 mg eluxadoline group and 25.1% in the 100 mg eluxadoline group achieved responder status in the 12-week interval compared with 17.1% in the placebo group (6.8% and 8.0% differences in the 75 mg eluxadoline group and the 100 mg eluxadoline group versus placebo, respectively), with the differences between groups being statistically significant; no calculation of confidence interval was available. For the same 12-week interval in IBS-3002, there was a higher percentage of responders in the eluxadoline groups: 28.9% in the 75 mg group, 29.6% in the 100 mg group, and 16.2% in the placebo group, also with statistically significant differences compared with placebo (12.7% and 13.4% differences in the 75 mg eluxadoline group and the 100 mg eluxadoline

group versus placebo, respectively). On the time interval of one to 26 weeks, 23.4% of patients in the 75 mg eluxadoline group and 29.3% in the 100 mg eluxadoline group achieved responder status compared with 19.0% responders in the placebo group (4.4% and 10.0% differences in the 75 mg eluxadoline group and the 100 mg eluxadoline group versus placebo, respectively), with the differences between the 75 mg eluxadoline group and placebo group not achieving statistical significance and the difference between the 100 mg eluxadoline group and placebo group achieving statistical significance; no calculation of confidence interval was available. For the same 26-week time interval in IBS-3002, there was a higher percentage of responders in the active eluxadoline groups: 30.4% in the 75 mg group, 32.7% in the 100 mg group, and 20.2% in the placebo group, also with statistically significant differences compared with placebo (10.2% and 12.5% differences in the 75 mg eluxadoline group and the 100 mg eluxadoline group versus placebo, respectively). An overview of the primary efficacy result, along with pooled results is presented in Table 11.

Sensitivity analyses for worst-case scenarios (in which missing data were included, and patients had to be a responder on 42 of 84 days for the 12-weeks period and 91 out of 182 days for the 26-weeks period regardless of diary compliance, with missing entries resulting in a nonresponder status for that day) that applied two-week definitions for responding as opposed to daily, and used a subset of patients with no dose interruption, were similar to the base case. Additional post hoc sensitivity analyses were conducted to assess the impact of rescue medication, and the impact of diary language also showed similar results to the primary analysis. Planned subgroups analyses for gender showed similar results to the base-case primary outcome analysis for both men and women.

A post hoc subgroup analysis of patients with a previous history of loperamide use was published in the literature.[15] The subgroup analysis stratified patients who reported loperamide use in the year prior to study enrolment into those that reported adequate symptom control on loperamide use and those that did not.[15] The overall results show a higher percentage of responders in patients who reported adequate symptom control on loperamide than in patients who reported no adequate symptom control. However, comparisons versus placebo show a statistically significant difference in the group that reported no adequate symptom control, while only the comparisons between the 100 mg eluxadoline-treated group of patients who reported adequate symptom control with previous use of loperamide versus placebo showed a statistically significant difference. Specifically, at the 26-week interval, of patients who reported adequate symptom relief with loperamide use in the previous year, 36.5%, 44.3%, and 26.7% were responders in the 75 mg eluxadoline group, the 100 mg eluxadoline group, and the placebo group, respectively, with a statistically significant difference of 17.6% between the 100 mg and the placebo groups. On the other hand, during the same interval, of patients who reported no adequate relief when they used loperamide in the previous year, 26.8%, 31.6%, and 17.5% were responders in the 75 mg eluxadoline group, the 100 mg eluxadoline group, and the placebo groups, respectively, with statistically significant differences of 9.3% and 14.1% between the 75 mg eluxadoline group and the placebo group, and the 100 mg eluxadoline group and the placebo group, respectively.

Table 8: Composite Responders – Primary Efficacy Outcome

Interval/Treatment	Composite Responders (Pain and Stool Consistency), ITT Population							
	IBS-3001				IBS-3002			
	N	Responder n (%)	Difference vs. placebo[a]	*P* value	N	Responder n (%)	Difference vs. placebo[a]	*P* value
Weeks 1–12 (FDA primary end point)								
Eluxadoline 75 mg b.i.d.	427	102 (23.9)	6.8%	**0.014**	381	110 (28.9)	12.7%	**< 0.001**
Eluxadoline 100 mg b.i.d.	426	107 (25.1)	8.0%	**0.004**	382	113 (29.6)	13.4%	**< 0.001**
Placebo b.i.d.	427	73 (17.1)	–	–	382	62 (16.2)	–	–
Weeks 1–26 (EMA primary end point)								
Eluxadoline 75 mg b.i.d.	427	100 (23.4)	4.4%	0.112	381	116 (30.4)	10.2%	**0.001**
Eluxadoline 100 mg b.i.d.	426	125 (29.3)	10.3%	**< 0.001**	382	125 (32.7)	12.5%	**< 0.001**
Placebo b.i.d.	427	81 (19.0)	–	–	382	77 (20.2)	–	–

Interval/Treatment	Pooled Results			
	N	Responder %	Difference vs. placebo[a]	*P* value
Weeks 1–12 (FDA primary end point)				
Eluxadoline 75 mg b.i.d.	808	26.2%	9.5%	**< 0.001**
Eluxadoline 100 mg b.i.d.	806	27.0%	10.3%	**< 0.001**
Placebo b.i.d.	809	16.7%	–	–
Weeks 1–26 (EMA primary end point)				
Eluxadoline 75 mg b.i.d.	808	26.7%	7.2%	**< 0.001**
Eluxadoline 100 mg b.i.d.	806	31.0%	11.5%	**< 0.001**
Placebo b.i.d.	809	19.5%	–	–

b.i.d. = twice daily; EMA = European Medicines Agency; ITT = intention to treat.

Note: Bold *P* values indicate statistical significance.

[a] Difference versus placebo was calculated by Health Canada reviewer in the Health Canada Reviewer's Report.

Source: IBS-3001 and 3002 clinical study reports[20,21] and Health Canada Reviewer's Report.[18]

Stool Consistency

Stool consistency (BSS) responders, a secondary outcome in both studies, were not adjusted for multiple testing. Stool consistency responders showed a statistically significant difference between eluxadoline and placebo in all comparisons except in the 26-week interval in the comparison between the 75 mg eluxadoline group and the placebo group in IBS-3001. Specifically, at the 12-week interval, IBS-3001 reported 30.0% responders in the 75 mg eluxadoline group, 34.3% responders in the 100 mg eluxadoline group, and 22.0% responders in the placebo group, while IBS-3002 reported 37.0% responders in the 75 mg eluxadoline group, 35.6% responders in the 100 mg eluxadoline group, and 20.9% responders in the placebo group. During the 26-week interval, IBS-3001 reported 28.1% responders in the 75 mg eluxadoline group, 34.0% responders in the 100 mg eluxadoline group, and a 24.1% responders in the placebo group, while IBS-3002 reported 34.4% responders in the 75 mg eluxadoline group, 39.8% responders in the 100 mg eluxadoline group, and 23.6% responders in the placebo group. A summary of the stool consistency responders outcome is presented in (Table 9).

Table 9: Stool Consistency Responder (Secondary Outcome)

Interval/ Treatment	Stool Consistency (BSS) Responders, ITT Population							
	IBS-3001				IBS-3002			
	N	Responder n (%)	Nonresponder n (%)	*P* value	N	Responder n (%)	Nonresponder n (%)	*P* value
Weeks 1–12								
Eluxadoline 75 mg b.i.d.	427	128 (30.0)	299 (70.0)	**0.008**	381	141 (37.0)	240 (63.0)	**< 0.001**
Eluxadoline 100 mg b.i.d.	426	146 (34.3)	280 (65.7)	**< 0.001**	382	136 (35.6)	246 (64.4)	**< 0.001**
Placebo b.i.d.	427	94 (22.0)	333 (78.0)	–	382	80 (20.9)	302 (79.1)	–
Weeks 1–26								
Eluxadoline 75 mg b.i.d.	427	120 (28.1)	307 (71.9)	0.186	381	131 (34.4)	250 (65.6)	**< 0.001**
Eluxadoline 100 mg b.i.d.	426	145 (34.0)	281 (66.0)	**0.001**	382	152 (39.8)	230 (60.2)	**< 0.001**
Placebo b.i.d.	427	103 (24.1)	324 (75.9)	–	382	90 (23.6)	292 (76.4)	–

Interval/ Treatment	Stool Consistency (BSS) Responders, ITT Population			
	Pooled Results			
	N	Responder n (%)	Difference vs. placebo	*P* value
Weeks 1–12				
Eluxadoline 75 mg b.i.d.	808	269 (33.3)	11.8%	**< 0.001**
Eluxadoline 100 mg b.i.d.	806	280 (34.7)	13.2%	**< 0.001**
Placebo b.i.d.	809	174 (21.5)	–	–
Weeks 1–26				
Eluxadoline 75 mg b.i.d.	808	251 (31.1)	7.2%	**< 0.001**
Eluxadoline 100 mg b.i.d.	806	297 (36.8)	12.9%	**< 0.001**
Placebo b.i.d.	809	193 (23.9)	–	–

b.i.d. = twice daily; BSS = Bristol stool scale; ITT = intention to treat.

Note: Bold *P* value indicates statistical significance.

[a] Difference versus placebo was calculated by Health Canada reviewer in the Health Canada Reviewer's Report.

Source: IBS-3001 and 3002 clinical study reports[20,21] and Health Canada Reviewer's Report.[18]

Abdominal Pain Intensity

Abdominal pain intensity was measured as pain responders in the included studies. This was a secondary outcome in both studies and was not adjusted for multiple testing. Pain responders showed no statistically significant differences between eluxadoline and placebo in either study. In the interval of weeks 1 through 26, 46.3%, 48.3%, and 44.0% were determined as responders in the 75 mg, 100 mg, and placebo pooled groups, respectively. By individual study, at the 12-week interval, IBS-3001 reported 30.0% pain responders in the 75 mg eluxadoline group, 34.3% pain responders in the 100 mg eluxadoline group, and a 22.0% responders in the placebo group, while IBS-3002 reported 37.0% responders in the 75 mg eluxadoline group, 35.6% responders in the 100 mg eluxadoline group, and

20.9% responders in the placebo group. During the 26-week interval, IBS-3001 reported 28.1% pain responders in the 75 mg eluxadoline group, 34.0% pain responders in the 100 mg eluxadoline group, and 24.1% responders in the placebo group, while IBS-3002 reported 34.4% responders in the 75 mg eluxadoline group, 39.8% responders in the 100 mg eluxadoline group, and 23.6% responders in the placebo group (Table 10).

The manufacturer reported conducting an analysis of the abdominal pain responder outcome using a response threshold of 40% and 50% instead of a 30% improvement from baseline. This analysis was not part of the original protocol and is considered a post hoc analysis, as outlined in the Health Canada Reviewer's Report.[18] The results of this post hoc analysis have not been reported here due to the high degree of uncertainty associated with the analysis.

Table 10: Abdominal Pain Responder (Secondary Outcome)

Interval/Treatment	Pain Responders, ITT Population							
	IBS-3001				IBS-3002			
	N	Responder n (%)	Nonresponder n (%)	*P* value	N	Responder n (%)	Nonresponder n (%)	*P* value
Weeks 1–12								
Eluxadoline 75 mg b.i.d.	427	181 (42.4)	246 (57.6)	0.404	381	183 (48.0)	198 (52.0)	0.448
Eluxadoline 100 mg b.i.d.	426	184 (43.2)	242 (56.8)	0.284	382	195 (51.0)	187 (49.0)	0.111
Placebo b.i.d.	427	169 (39.6)	258 (60.4)	–	382	173 (45.3)	209 (54.7)	–
Weeks 1–26								
Eluxadoline 75 mg b.i.d.	427	193 (45.2)	234 (54.8)	0.582	381	181 (47.5)	200 (52.5)	0.448
Eluxadoline 100 mg b.i.d.	426	198 (46.5)	228 (53.5)	0.355	382	191 (50.0)	191 (50.0)	0.148
Placebo b.i.d.	427	185 (43.3)	242 (56.7)	–	382	171 (44.8)	211 (55.2)	–

Interval/Treatment	Pain Responders, ITT Population Pooled Results			
	N	Responder n (%)	Difference vs. placebo	*P* value
Weeks 1–12				
Eluxadoline 75 mg b.i.d.	808	364 (45.0)	2.7%	0.261
Eluxadoline 100 mg b.i.d.	806	377 (46.8)	4.5%	0.069
Placebo b.i.d.	809	342 (42.3)	–	–
Weeks 1–26				
Eluxadoline 75 mg b.i.d.	808	374 (46.3)	2.3%	0.357
Eluxadoline 100 mg b.i.d.	806	389 (48.3)	4.3%	0.086
Placebo b.i.d.	809	356 (44.0)	–	

b.i.d. = twice daily; ITT = intention to treat.

Note: Bold *P* value indicates statistical significance.

[a] Difference versus placebo was calculated by Health Canada reviewer in the Health Canada Reviewer's Report.

Source: IBS-3001 and 3002 clinical study reports[20,21] and Health Canada Reviewer's Report.[18]

Frequency of Bowel Movement

Risk ratio of bowel movement frequency was reported as a secondary outcome in both studies and was not adjusted for multiple testing. Bowel movement frequency showed a [redacted] difference between [redacted]. In IBS-3001, at 12 weeks, the risk ratio was [redacted] and [redacted] between the 75 mg eluxadoline arm, the 100 mg eluxadoline

arm, and placebo, respectively. At 26 weeks the risk ratio was [redacted] and [redacted] between the 75 mg eluxadoline arm, the 100 mg eluxadoline arm, and placebo, respectively. In IBS-3002, at 12 weeks, the risk ratio was [redacted] and [redacted] between the 75 mg eluxadoline arm, the 100 mg eluxadoline arm, and placebo, respectively. At 26 weeks the risk ratio was [redacted] and [redacted] between the 75 mg eluxadoline arm, the 100 mg eluxadoline arm, and placebo, respectively. A summary of the frequency of bowel movement outcome is presented in (Table 11).

Table 11: Bowel Movement Frequency (Secondary Outcome)

Interval/Treatment	Bowel Frequency							
	IBS-3001				IBS-3002			
	Risk	Risk ratio	95% CI	*P* value	Risk	Risk ratio	95% CI	*P* value
Weeks 12								
Eluxadoline 75 mg b.i.d.	[redacted]							
Eluxadoline 100 mg b.i.d.	[redacted]							
Placebo b.i.d.	[redacted]							
Weeks 26								
Eluxadoline 75 mg b.i.d.	[redacted]							
Eluxadoline 100 mg b.i.d.	[redacted]							
Placebo b.i.d.	[redacted]							

b.i.d. = twice daily; CI = confidence interval.

Note: Bold *P* values indicate statistical significance.

[a] Difference versus placebo was calculated by Health Canada reviewer in the Health Canada Reviewer's Report.

Source: IBS-3001 and 3002 clinical study reports[20,21] and Health Canada Reviewer's Report.[18]

Other Efficacy Outcomes

Relief of IBS Symptoms

Abdominal discomfort: The least squares mean difference of the abdominal discomfort score was reported as a secondary outcome in both studies and was not adjusted for multiple testing. The least squares mean difference showed a statistically significant difference between eluxadoline and placebo in all comparisons. In IBS-3001, at 12 weeks, the least squares mean difference was −0.28 (95% CI, −0.54 to −0.02) and −0.34 (95% CI, −0.60 to 0−.08) between the 75 mg eluxadoline arm and placebo and between the 100 mg eluxadoline arm and placebo, respectively. At 26 weeks the least square mean difference was −0.40 (95% CI, −0.67 to −0.14) and −0.37 (95% CI, −0.64 to −0.11) between the 75 mg eluxadoline arm and placebo and between the 100 mg eluxadoline arm and placebo, respectively. In IBS-3002, at 12 weeks, the least squares mean difference was −0.32 (95% CI, −0.59 to −0.04) and −0.36 (95% CI, −0.63 to −0.08) between the 75 mg eluxadoline arm and placebo and between the 100 mg eluxadoline arm and placebo, respectively. At 26 weeks the least squares mean difference was −0.33 (95% CI, −0.60 to −0.05) and −0.50 (95% CI, −0.77 to −0.22) between the 75 mg eluxadoline arm and placebo and between the 100 mg eluxadoline arm and placebo, respectively. A summary of the abdominal discomfort outcome is presented in Table 12.

Urgency: Risk ratio of urgency episodes was reported as a secondary outcome in both studies and was not adjusted for multiple testing. Urgency episodes showed a statistically significant difference between eluxadoline and placebo in all comparisons. In IBS-3001, at 12 weeks, the risk ratio was 0.78 (95% CI, 0.68 to 0.90) and 0.80 (95% CI, 0.69 to 0.92) between the 75 mg eluxadoline arm and placebo and between the 100 mg eluxadoline arm and placebo, respectively. At 26 weeks the risk ratio was 0.78 (95% CI, 0.67 to 0.90) and 0.84 (95% CI, 0.72 to 0.97) between the 75 mg eluxadoline arm and placebo and between the 100 mg eluxadoline arm and placebo, respectively. In IBS-3002, at 12 weeks, the risk ratio was 0.64 (95% CI, 0.53 to 0.77) and 0.85 (95% CI, 0.54 to 0.78) between the 75 mg eluxadoline arm and placebo and between the 100 mg eluxadoline arm and placebo, respectively. At 26 weeks the risk ratio was 0.61 (95% CI, 0.50 to 0.73) and 0.61 (95% CI, 0.51 to 0.73) between the 75 mg eluxadoline arm and placebo and between the 100 mg eluxadoline arm and placebo, respectively. A summary of urgency episodes outcome is presented in Table 12.

Unpredictability: No measure of unpredictability was reported in the studies.

Activities of daily living: No measure of activities of daily living was reported in the studies.

Health-Related QoL: Health-related QoL was measured using the IBS-QoL questionnaire. The outcome was secondary in nature and not adjusted for multiple comparisons. The outcome was measured in two ways: the least squares means difference and the percentage of responders using the MCID value of a 14-point difference. Overall, comparisons using the least squares mean difference showed a statistically significant difference between the active groups and placebo except at week 26 and week 30 in the 100 mg eluxadoline arm in IBS-3002. However, when using the MCID definition to determine responders, no statistically significant differences were found in either study except in the eluxadoline 100 mg group at week 52 in IBS-3001. A summary of IBS-QoL outcomes is presented in (Table 12).

Table 12: Other Efficacy Outcomes

Interval/Treatment	IBS-D Global Symptom Responders							
	IBS-3001				IBS-3002			
	N	Responder n (%)	Nonresponder n (%)	*P* value	N	Responder n (%)	Nonresponder n (%)	*P* value
Weeks 1–12								
Eluxadoline 75 mg b.i.d.	[redacted]							
Eluxadoline 100 mg b.i.d.	[redacted]							
Placebo b.i.d.	[redacted]							
Weeks 1–26								
Eluxadoline 75 mg b.i.d.	[redacted]							
Eluxadoline 100 mg b.i.d.	[redacted]							
Placebo b.i.d.	[redacted]							

Interval/Treatment	IBS-D Adequate Relief Responders, ITT Population							
	IBS-3001				IBS-3002			
	N	Responder n (%)	Nonresponder n (%)	*P* value	N	Responder n (%)	Nonresponder n (%)	*P* value
Weeks 12								
Eluxadoline 75 mg b.i.d.	[redacted]							
Eluxadoline 100 mg b.i.d.	[redacted]							
Placebo b.i.d.	[redacted]							
Weeks 26								
Eluxadoline 75 mg b.i.d.	[redacted]							
Eluxadoline 100 mg b.i.d.	[redacted]							
Placebo b.i.d.	[redacted]							

Interval/Treatment	Abdominal Discomfort Score, ITT Population							
	IBS-3001				IBS-3002			
	LS mean	LS mean difference	95% CI	*P* value	LS Mean	LS mean difference	95% CI	*P* value
Week 12								
Eluxadoline 75 mg b.i.d.	[redacted]							
Eluxadoline 100 mg b.i.d.	[redacted]							
Placebo b.i.d.	[redacted]							

Interval/Treatment	Abdominal Discomfort Score, ITT Population							
	IBS-3001				IBS-3002			
Week 26								
Eluxadoline 75 mg b.i.d.	[redacted]							
Eluxadoline 100 mg b.i.d.	[redacted]							
Placebo b.i.d.	[redacted]							

Interval/Treatment	Number of Urgency Episodes							
	IBS-3001				IBS-3002			
	Risk	Risk ratio	95% CI	*P* value	Risk	Risk ratio	95% CI	*P* value
Week 12								
Eluxadoline 75 mg b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eluxadoline 100 mg b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 26								
Eluxadoline 75 mg b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eluxadoline 100 mg b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Interval/Treatment	IBS-QoL Total Scores, ITT Population							
	IBS-3001				IBS-3002			
	LS mean	LS mean difference	95% CI	*P* value	LS mean	LS mean difference	95% CI	*P* value
Weeks 12								
Eluxadoline 75 mg b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eluxadoline 100 mg b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weeks 26								
Eluxadoline 75 mg b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eluxadoline 100 mg b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weeks 30								
Eluxadoline 75 mg b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eluxadoline 100 mg b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weeks 52								
Eluxadoline 75 mg b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eluxadoline 100 mg b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Interval/Treatment	IBS-QoL Total Score Responder, ITT Population							
	IBS-3001				IBS-3002			
	N	Responder n (%)	Nonresponder n (%)	*P* value	N	Responder n (%)	Nonresponder n (%)	*P* value
Weeks 12								
Eluxadoline 75 mg b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eluxadoline 100 mg b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weeks 26								
Eluxadoline 75 mg b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eluxadoline 100 mg b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weeks 30								
Eluxadoline 75 mg b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eluxadoline 100 mg b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weeks 52								
Eluxadoline 75 mg b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eluxadoline 100 mg b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo b.i.d.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b.i.d. = twice daily; CI = confidence interval; IBS-QoL = Irritable Bowel Syndrome Quality of Life questionnaire; ITT = intention to treat; LS = least squares.

Note: Bold *P* value indicates statistical significance.

Source: IBS-3001 and 3002 clinical study reports.[20,21]

Harms

Only those harms identified in the review protocol are reported below (see the Protoco sectionl).

Adverse Events

Overall, 60.5%, 55.3%, and 55.5% of patients in the eluxadoline 75 mg, eluxadoline 100 mg, and placebo groups, respectively, of IBS-3001 experienced at least one adverse event. Similarly, 59.9%, 61.8%, and 55.9% of patients in the 75 mg, 100 mg, and placebo groups, respectively, of IBS-3002 experienced at least one adverse event. Constipation was the most common adverse event in the eluxadoline treatment groups and occurred in more patients than in the placebo groups. Nausea was another adverse event that occurred in a higher percentage of patients in the eluxadoline groups compared with placebo groups. Other adverse events occurred in a similar percentage of patients between treatment groups.

Serious Adverse Events

Overall, 5.8%, 5.6%, and 3.7% of patients in the eluxadoline 75 mg, eluxadoline 100 mg, and placebo groups, respectively, of IBS-3001 experienced at least one serious adverse event. For IBS-3002, 2.4%, 3.7%, and 2.1% of patients in the 75 mg, 100 mg, and placebo groups, respectively, experienced at least one adverse event. Serious adverse events were

experienced at a higher percentage in the eluxadoline groups in IBS-3001 than in the placebo group. IBS-3002 showed similar percentages of patients between groups with at least one serious adverse event. No single serious adverse had a frequency of greater than 1%.

Withdrawals Due to Adverse Events

In IBS-3001, the withdrawals due to adverse events were reported at 8.2%, 9.6%, and 3.7% for the 75 mg, 100 mg, and the placebo groups, respectively. In IBS-3002 the withdrawals due to adverse events were reported at 8.4%, 7.4%, and 5.0% for the 75 mg, 100 mg, and the placebo groups, respectively. Constipation and abdominal pain were the two most common reasons for discontinuation.

Mortality

One death was reported in IBS-3001 in a patient that was originally randomized to the 75 mg eluxadoline treatment group but withdrew two days before passing away. The last dose of eluxadoline the patient received was 21 days before passing away. The patient's death was determined to be due to arteriosclerosis coronary artery disease and was not treatment-related.

Notable Harms

In IBS-3001 and IBS-3002, pancreatitis or acute pancreatitis was reported in seven patients, all of whom were in the eluxadoline treatment groups. Adverse events that were used to assess drug dependency did not show any marked discrepancy to placebo and were of a small percentage. IBS-3002 administered the SOWS tool to participants who completed the double-blind treatment period and entered the single-blind four-week withdrawal phase. The numeric scores were low and were similar across groups, with a median of 4.0, 5.5, and 5.0 for the 75 mg, 100 mg, and placebo groups, respectively. IBS-3001 also administered the SOWS questionnaire on the last follow-up visit. Similar to IBS-3002, the numeric scores were low and were similar across groups, with a median of 2.0, 3.0, and 3.0 for the 75 mg, 100 mg, and placebo groups, respectively.

Patients with prior cholecystectomy had higher percentages of having at least one adverse event when compared with the full study population in IBS-3001: 73.8%, 72.5%, and 79.8% of patients with cholecystectomy experienced at least one adverse event in each of the 75 mg eluxadoline group, 100 mg eluxadoline group, and placebo group, respectively. In IBS-3002, percentages of patients with cholecystectomy were also higher than the full study population; 70.4%, 70.3%, and 73.9% of patients with cholecystectomy experienced at least one adverse event in each of the 75 mg eluxadoline group, 100 mg eluxadoline group, and placebo group, respectively.

Table 13: Harms

	IBS-3001 (Safety Analysis Set)			IBS-3002 (Safety Analysis Set)		
	Eluxadoline 75 mg b.i.d. N = 428	Eluxadoline 100 mg b.i.d. N = 479	Placebo b.i.d. N = 427	Eluxadoline 75 mg b.i.d. N = 379	Eluxadoline 100 mg b.i.d. N = 380	Placebo b.i.d. N = 381
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with > 0 AEs, N (%)						
Most common AEs[a]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE potentially related to abuse						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	IBS-3001 (Safety Analysis Set)			IBS-3002 (Safety Analysis Set)		
	Eluxadoline 75 mg b.i.d. N = 428	Eluxadoline 100 mg b.i.d. N = 479	Placebo b.i.d. N = 427	Eluxadoline 75 mg b.i.d. N = 379	Eluxadoline 100 mg b.i.d. N = 380	Placebo b.i.d. N = 381
[redacted]						
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[redacted]						
[redacted]						
[redacted]						
[redacted]						
GI AEs by prior cholecystectomy status						
[redacted]						
[redacted]						
SAEs						
Patients with > 0 SAEs, N (%)						
Most common SAEs[a]						
WDAEs						
WDAEs, N (%)						
Most common reasons						
[redacted]						
[redacted]						
Deaths						
Number of deaths, N (%)						
Most common reasons						
[redacted]						
Notable harms						
Pancreatitis						
Acute pancreatitis						

AE = adverse event; b.i.d. = twice daily; GI = gastrointestinal; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Frequency > 1%.

Source: IBS-3001 and 3002 clinical study reports.[20,21]

Discussion

Summary of Available Evidence

Two phase III, double-blind, randomized, placebo-controlled, parallel-group, superiority studies (IBS-3001 and IBS-3002) were included in this CDR review. Investigators randomized 1,281 (IBS-3001) and 1,146 (IBS-3002) IBS-D patients (Rome III criteria) to 75 mg twice-daily eluxadoline, 100 mg twice-daily eluxadoline, and placebo groups in a 1:1:1 ratio. The primary outcome in both studies was a composite of pain and stool consistency responders at 12 weeks (FDA end point requirement) or 26 weeks (EMA end point requirement). Both studies were identical in design except that IBS-3001 included an additional 26 weeks of double-blind treatment with a subsequent two weeks of follow-up, while IBS-3002 included an additional four weeks of a single-blinded withdrawal period.

Interpretation of Results

Efficacy

The composite primary outcome defined a responder as a patient who achieved a responder status for both worst abdominal pain AND stool consistency using the BSS. For each component, the patient had to have reported improvement of 30% or more compared with prescreening on 50% or more of the days in the interval of interest. In IBS-3001, 23.9% of patients in the 75 mg eluxadoline group and 25.1% in the 100 mg eluxadoline group achieved responder status in the 12-week interval compared with 17.1% in the placebo group (6.8% and 8.0% differences in the 75 mg eluxadoline group and the 100 mg eluxadoline group versus placebo, respectively), with the differences between groups statistically significant. For the same 12-week interval in IBS-3002, there were higher percentages of responders in the eluxadoline groups: 28.9% in the 75 mg group, 29.6% in the 100 mg group, and 16.2% in the placebo group, also with statistically significant differences compared with placebo (12.7% and 13.4% differences in the 75 mg eluxadoline group and the 100 mg eluxadoline group versus placebo, respectively). On the time interval of one to 26 weeks, 23.4% of patients in the 75 mg eluxadoline group and 29.3% in the 100 mg eluxadoline group achieved responder status in the 26-week interval compared with 19.0% responders in the placebo group (4.4% and 10.0% differences in the 75 mg eluxadoline group and the 100 mg eluxadoline group versus placebo, respectively), with the differences between the 75 mg eluxadoline group and placebo group not achieving statistical significance and the difference between the 100 mg eluxadoline group and placebo group achieving statistical significance. For the same 26-week time interval in IBS-3002, there were higher percentages of responders in the active eluxadoline groups; 30.4% in the 75 mg group, 32.7% in the 100 mg group, and 20.2% in the placebo group, also with statistically significant differences compared with placebo (10.2% and 12.5% differences in the 75 mg eluxadoline group and the 100 mg eluxadoline group versus placebo, respectively). The pooled results from both trials during the interval of one to 12 weeks show that 26.2%, 27.0%, and 16.7% achieved the definition of a responder in each of the 75 mg, 100 mg, and placebo groups, respectively, with statistically significant differences compared with placebo. For the one- to 26-weeks interval, the pooled results show that 26.7%, 31.0%, and 19.5% achieved the definition of a responder in each of the 75 mg, 100 mg, and placebo groups, respectively, with statistically significant differences compared with placebo.

Sensitivity analyses results for the primary outcome were similar to the primary analysis. Subgroup analyses of gender show results similar to the primary analysis. A post hoc subgroup analysis of patients with a previous history of loperamide-stratified patients who reported loperamide use in the year prior to study enrolment into those that reported adequate symptom control on loperamide use and those that did not.[15] The overall results show a higher percentage of responders in patients that reported adequate symptom control on loperamide than in patients who reported no adequate symptom control. However, comparisons versus placebo show a statistically significant difference in the group that reported no adequate symptom control, while only the comparisons between the 100 mg eluxadoline-treated group of patients that reported adequate symptom control with previous use of loperamide versus the placebo group showed a statistically significant difference. However, the results of this subgroup analysis are uncertain as this subgroup analysis was not pre-specified in the protocol section of the submitted clinical study reports of either study. In addition, identification of patients and stratification based on potential recall of symptom control in the past year are susceptible to recall bias. Moreover, the subgroup analysis, with further stratification, is no longer considered representative of a randomized population and no baseline characteristics were reported to allow assessment of potential imbalances in group population.

A breakdown of the primary outcome to its individual components was reported in the studies as secondary outcomes. The worst abdominal pain results did not show any significant differences between eluxadoline and placebo groups in either study or the pooled results. The stool consistency results show statistically significant differences, suggesting that the benefit on the primary outcomes is largely driven by the effect of eluxadoline on diarrhea rather than on pain. Additional exploratory outcomes support the beneficial effect observed in the primary outcome.

Although the primary outcome reported in the study was in accordance with regulatory guidance, input from patients suggest a greater emphasis on the ability to engage in social activities and lead a normal, independent, and mobile life. In addition, the clinical expert consulted by CDR for this review indicated that the primary outcome is not commonly used in clinical practice. While the studies did include a measure of QoL with IBS-QoL and a measure of the number of urgency episodes, both were secondary outcomes that were not controlled for multiple statistical testing. An adjustment for multiple testing could have provided a greater certainty once the treatment effect was observed in these secondary outcomes. More relevant outcomes, such as the IBS-QoL measure, did not show any statistically significant differences when considering the MCID value as a definition of a responder. Other outcomes such as the adequate relief and global symptoms scales lack validation, an MCID, and adjustment for multiple testing. This lack of strong evidence in outcomes of concern to patients creates uncertainty in establishing the clinical significance of eluxadoline in patients with IBS-D.

The overall evidence from the included studies suggests a beneficial pharmacological effect of eluxadoline over placebo. However, only one-third of patients achieved responder status (26.7% in the pooled 75 mg eluxadoline, 31.0% in the pooled 100 mg eluxadoline during the one- to 26-weeks interval) and the difference versus placebo was approximately 10% (7.2% difference in the pooled 75 mg eluxadoline, and 11.5% difference in the pooled 100 mg eluxadoline during the one- to 26-weeks interval), suggesting that the clinical benefit that eluxadoline would bring into the existing pharmacological treatment approaches (e.g., treatment of diarrhea) in the IBS patient population is uncertain.

Furthermore, uncertainties regarding the clinical benefit of the observed treatment effect are also augmented with the following points:

- Lack of an MCID for the worst abdominal pain score, the stool consistency score, and the resulting composite outcome (i.e., an established MCID using anchor-based methods, distribution-based methods, or a Delphi questionnaire) was evident.
- Because of the inherit nature of the clinical value of symptomatic management, a large number of responders would prefer to be shown that the drug has added clinical benefit to provide to the general IBS-D population.[18]
- The composite outcome measure was recognized as not being used in clinical practice. This further reduced our ability to extrapolate the added clinical benefit that eluxadoline could provide to the general IBS-D population. Although both studies used other outcomes to assess common approaches in patient management (e.g., global symptom score, discomfort score, adequate relief), these tools lack validation and an established MCID.

In addition to the uncertainty surrounding the clinical benefit of the observed treatment effect, the lack of active comparison affects our ability to make a comparative assessment of eloxadoline versus commonly used drugs. While there is no Health Canada–approved medication for the treatment of IBS-D, loperamide is commonly used to manage symptoms of diarrhea in IBS-D patients and its use is supported by clinical guidance documents from National Institute for Health and Care Excellence and the American Gastroenterological Association.[8,13] No indirect evidence was found to help support an assessment of the comparative evidence of eluxdoline versus other commonly used drugs such as loperamide.

Harms

Overall, the most common adverse events reported in both studies were constipation and abdominal pain. Seven incidents of pancreatitis or acute pancreatitis were observed in the eluxadoline arms but not in the placebo arms. In addition, most cases of pancreatitis or acute pancreatitis were observed in patients without a gallbladder. The FDA issued a drug safety communication discouraging the use of eluxadoline in patients without a gallbladder.[25] The Health Canada Reviewer's Report indicated that the abuse potential of eluxadoline is low, but not null.[18] Also, while the assessment of abuse potential was conducted for the oral route, the manufacturer did not limit the possibility of illicit use of eluxadoline and the abuse potential if administered intravenously through injection or intranasally through snorting powder from crushed tablet. The Health Canada Reviewer's Report noted that higher adverse events were seen in patients 65 years and older and that these patients should be given the 75 mg eluxadoline dose.

Potential Place in Therapy[b]

First-line management of IBS-D is focused on behavioural advice, including suggesting dietary changes, emphasizing psychological well-being, and providing reassurance as to the benign nature of the syndrome. While medications are commonly used for symptoms of IBS-D, including antidiarrheals, tricyclic antidepressants, and antispasmotics, there is minimal evidence for their effectiveness in the short- or long-term. It is likely that the introduction of eluxadoline will initially generate some degree of excitement among

[b] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

prescribers and patients who are hopeful that this medication represents the long-sought cure for their symptoms.

Given the mean age of onset of IBS-D at a relatively young age and the lack of a cure, a large number of patients have already tried a number of different drugs, the effects of which were either absent or at best transient, incomplete, and inconsistent. Therefore, it is likely that eluxadoline would be used by patients who have persistent or recalcitrant symptoms that multiple other drugs have failed to alleviate.

For relatively new cases of IBS-D, it is more difficult to define how this medication will be used compared with other therapies. In cases where drug therapy is used, eluxadoline will likely be used primarily when other antidiarrheal drugs (loperamide, diphenoxylate), which are less expensive and more familiar, have failed to provide adequate relief. However, the clinical expert consulted suspects that this class of drugs will be less efficacious, as these patients have already shown a lack of efficacy to other medications that activate opioid receptors.

For patients with IBS-D who also have a predominant component of abdominal pain or patients for whom pain is the symptom most negatively affecting QoL, it is likely that eluxadoline would be used when current therapies such as tricyclic antidepressants have failed. In patients where tricyclic antidepressants have been completely ineffective or where use is limited by side effects, eluxadoline may be used instead; it may be used as a concurrent medication in patients with partial response.

The duration of therapy is likely to vary among patients. Given the relatively low response rates in the randomized controlled trials relative to placebo, as well as the relatively small magnitude of effect on abdominal pain specifically, eluxadoline is a medication that may have more subtle benefits in clinical practice. In clinical practice, patients with treatment-resistant symptoms are also highly likely to have concurrent mental health disease and personality traits that are strongly predictive of a lack of treatment response to any therapy. The clinical expert consulted for this review suspects that there will be a significant amount of short, circumscribed use and intermittent use, but relatively little long-term use. There is also the potential for eluxadoline to be a component of polypharmacy in the elderly and other personal care home residents, where it might be prescribed for episodic diarrhea and then never actively deprescribed.

As clinicians rarely make a positive diagnosis of IBS-D, eluxadoline is likely to be used off-label for patients who have abdominal symptoms (predominantly diarrhea symptoms) yet to do not meet official criteria for having IBS-D, or for patients with IBS-M who are in a diarrheal phase, or for whom diarrhea is the most troubling symptoms.

Conclusions

Two phase III, double-blind, randomized, placebo-controlled, parallel-group, trials (IBS-3001 and IBS-3002) were included in the CDR systematic review. Eluxadoline administered at 75 mg twice daily or 100 mg twice daily is statistically superior to placebo in patients with IBS-D based on the primary composite outcome of WAP score and stool consistency responders. The benefit of eluxadoline was primarily driven by stool consistency rather than the reduction of pain. Nearly two-thirds of the patients in the eluxadoline treatment groups were non-responders as per the definition of composite primary outcome. In addition, the difference in the percentage of responders in the eluxadoline group versus placebo was approximately 10%. There is no clear benefit on patients' QoL when measured as the percentage of patients who met the pre-specified MCID threshold. Additionally, there was unclear clinically significant benefit on other outcomes, such as urgency episodes, bowel movement frequency and abdominal discomfort. The most common adverse events reported were constipation and abdominal pain. A serious adverse event that was only recorded in eluxadoline-treated patients was pancreatitis or acute pancreatitis.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

One patient group responded to the call for patient input for this CDR review.

The Gastrointestinal (GI) Society patient group describes itself as a Canadian leader in providing trusted, evidence-based information on all areas of the GI tract. The society is committed to improving the lives of people with GI and liver conditions by supporting research, advocating for appropriate patient access to health care, and promoting GI and liver health. It provides educational resources for patients across Canada via information pamphlets, a quarterly newsletter, free lectures, and a “dynamic” website in both English and French. It also provides support group meetings for those newly diagnosed with a GI disorder, as well as those who have lived with a GI condition for years. The GI Society consists of highly trained staff and volunteers who offer additional patient resources, including responding to information requests and participating in community initiatives. Staff and advisors work closely with health care professionals, other patient groups, and governments at all levels on behalf of GI patients. The GI Society has supported clinical, basic, and epidemiological GI research.

The GI Society declared a receipt of financial support within the past two years from Allergan, which is the sponsor of the drug under review. The GI Society had no help from outside the group to collect and analyze data, or to complete the submission.

2. Condition-Related Information

The GI Society obtained information through printed sources, collective feedback from patients associated with the GI Society who suffer from diarrhea-predominant Irritable bowel syndrome (IBS-D), information written by physicians for their publications (newsletter, pamphlets, websites), and responses from an online survey of IBS patients with approximately 3,000 respondents.

The patient group describes IBS-D as a serious problem that significantly impairs quality of life, one in which sufferers face public stigma and a lack of understanding. It reported 13% to 20% of Canadians are living with IBS, which is a chronic, often debilitating, functional GI disorder, and approximately one-third of these have IBS-D. It is normal to have a bowel movement as frequently as three times a day or as infrequently as three times a week, provided the stool is soft and comfortable to pass. However, a person with IBS-D experiences frequent bowel movements, which can often be watery, along with bowel urgency, bloating, and abdominal pain. Almost everyone experiences diarrhea occasionally, but in IBS-D, this diarrhea is a frequent, painful occurrence. In this group of IBS patients, the digestive system contracts quickly, speeding up transit time for products of digestion.

The GI Society specifically mentioned that seniors, who are already often isolated due to health limitations, suffer further from IBS-D when they cannot participate in social interactions or maintain independence because they are worried about when they might suddenly need to access a washroom or experience severe abdominal pain.

The patient group stated that one of the most uncomfortable aspects of IBS-D is not knowing when symptoms might occur, which leads many individuals with IBS-D to avoid social gatherings and other outings, and causes feelings of embarrassment, self-consciousness, and being ashamed. This limitation on their social lives and time spent with family can be very isolating. Patients feel that IBS-D rules their lives as they have to plan their daily activities around toilets and how they are feeling that day. It limits their ability to function normally on a daily basis, including everyday activities such as driving, going to shows, working, and eating out. One patient reported, "[I] can't eat while working for fear of diarrhea and gas, so [I] become sluggish and get headaches when working." It was described by patients as not simply having diarrhea or the flu, as they will not just get over it. Another patient said eating is "not out of pleasure as it once was, it is now essential and painful." Further to that point, input from a different patient reported the loss of 20 pounds in about four weeks during the early stages of IBS-D because of an inability to eat anything without getting diarrhea. It was clear from the input received from various patients that living with IBS-D is exhausting, both physically and mentally.

3. Current Therapy-Related Information

The patient group reported that there are treatments available for IBS-D, but many patients do not respond to the available treatments. Diet and exercise, which includes eating regular well-balanced meals and snacks with high-fibre content, as set out in Canada's Food Guide, and maintaining an adequate fluid intake, are reported by the patient group to help many, but not all, individuals with IBS-D manage diarrhea. Further, certain types of fibre can help slow down the passage of stool, but this is often not enough for moderate to severe diarrhea. Pelvic dysfunction physiotherapy was also mentioned as a current therapy used or IBS-D, which may include bowel retraining, electrical stimulation, and posture correction that is helpful for some patients, but usually in combination with other treatments. In addition, antidiarrheal medications that work by altering the muscle activity of the intestine to slow down transit time are also used. Patients have expressed that these treatments become ineffective over time or did not work, and that the affordability of treatments and products is an issue.

4. Expectations About the Drug Being Reviewed

No direct patient experience with eluxadoline was reported. The GI Society simply stated that patients want medications that work for them. IBS is a highly individualized disorder, with an unknown cause, and each person reacts differently to various treatments. The society noted that the lack of available treatments impedes the ability of patients to meet the normal responsibilities of life at work, at home, and in the community, which makes going about day-to-day life normally without concern for when their next bout of diarrhea and pain will strike the most important objective for many IBS-D sufferers. It provided many personal quotes from patients who are overwhelmed and severely affected by ongoing, excessive diarrhea. Based on the description of the drug, the GI Society expects the patient population specifically affected by IBS-D will receive Viberzi enthusiastically and that it could fill a crucial treatment gap for IBS-D patients.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE ALL 1946 to present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 27, 2018
Alerts:	Weekly search updates until July 18, 2018
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
ppez	Ovid database code; MEDLINE ALL
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY
1. (eluxadoline* or viberzi* or truberzi* or jnj27018966 or jnj-27018966 or 45tpj4mbq1).ti,ab,ot,hw,rn,nm,kf.
2. 1 use medall
3. *eluxadoline/
4. (eluxadoline* or viberzi* or truberzi* or jnj27018966 or jnj-27018966 or 45tpj4mbq1).ti,ab,kw.
5. 3 or 4
6. 5 use oemezd
7. conference abstract.pt.
8. 6 not 7
9. 2 OR 8
10. remove duplicates

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	March 2018
Keywords:	Viberzi AND Irritable bowel syndrome
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
CROTEAU et al. (2017) Am J Gastroenterol 2017;112(10):1616, 2017	Study design
CASH et al. (2017) Am J Gastroenterol 2017;112(10):1619-20	Study design
FANT et al. (2017) Clin Gastroenterol Hepatol 2017;15(7):1021-9	Study design

Appendix 4: Validity Of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Score for worst abdominal pain (WAP) (composite response used for primary end point in IBS-3001 and IBS-3002)
- Bristol stool scale for (BSS) stool consistency (composite response used for primary end point in IBS-3001 and IBS-3002)
- Abdominal bloating score
- Abdominal discomfort score
- Irritable bowel syndrome with diarrhea (IBS-D) global symptom score
- Irritable Bowel Syndrome Quality of Life questionnaire (IBS-QoL)
- Adequate relief of IBS symptoms (IBS-AR)

Findings

The seven outcomes used to measure the treatment effect of IBS-D in this report have been summarized in Table 14.

Table 14: Summary of Outcome Measures and Evidence of Validation

Instrument	Type	Evidence of Validity	MCID	References
Worst abdominal pain (WAP) score	Patient-reported assessment of "worst abdominal pain" in the preceding 24 hours, 11-point ordinal scale from 0 to 10, with 0 representing no pain and 10 representing the worst imaginable pain.	No	Unknown	
Bristol stool scale (BSS)	BSS is a standardized method for classification of stool form, uses an ordinal scale from type 1 (hardest) to type 7 (softest), with types 1 and 2 considered abnormally hard/indicative of constipation, and types 6 and 7 being abnormally loose and liquid stools indicative of diarrhea.	Yes	Unknown	Blake et al. (2016)[24]
Abdominal bloating score	Patient-reported outcome used to assess abdominal bloating based on a 24-hour recall, rated on an ordinal scale from 0 to 10, with a higher score corresponding to more severe bloating and 10 being equal to the worst imaginable bloating.	No	Unknown	
Abdominal discomfort score	Assessment of abdominal discomfort based on a patient reported 24-hour recall, rated on an ordinal scale from 0 to 10, with a higher score corresponding to more severe abdominal discomfort and 10 being the worst imaginable discomfort.	No	Unknown	

Instrument	Type	Evidence of Validity	MCID	References
IBS-D global symptom score	Measures overall symptoms associated with IBS-D, is patient-reported based on 24-hour recall using a scale from 0 to 4 which corresponds to no symptoms, mild, moderate, severe and very severe symptoms, respectively.	No	Unknown	
34-item IBS-QoL	Patient-reported QoL questionnaire tailored to patients with IBS and also validated in patients with IBS-D, specifically. Includes 34 questions that are scored on a five-point Likert scale; questions can be divided into 8 subscales: dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual, and relationships.	Yes	14-point difference, based on a sample of female patients with FBD (79% of which was diagnosed with IBS)	Patrick et al. (1998) Drossman et al. (2000)[27] Drossman et al. (2007)[28] Andrae et al. (2013)[29]
Adequate relief of IBS symptoms (IBS-AR)	Patient-reported, dichotomous, single-item outcome; answer yes/no to the question, "Over the past week, have you had adequate relief of your IBS symptoms?"	No	Unknown	

BSS = Bristol stool scale; FBD = functional bowel disorder; IBS = Irritable bowel syndrome; IBS-AR = adequate relief of IBS symptoms; IBS-D = Irritable bowel syndrome with diarrhea; IBS-QoL = Irritable Bowel Syndrome Quality of Life questionnaire; MCID = minimal clinically important difference; QoL = quality of life; WAP = worst abdominal pain.

Score for Worst Abdominal Pain

The WAP score is a patient-reported outcome based on an 11-point ordinal scale from 0 to 10, with 0 representing no pain and 10 representing the worst imaginable pain.[20,21] The 11-point scale is used to evaluate a patient's "worst abdominal pain" experienced in the previous 24 hours based on patient recall.[20,21] No evidence of validity is identified for the WAP score, but it has been recommended as a co-primary end point in clinical trials for Irritable bowel syndrome (IBS), as it is a measure of one of the two major symptoms of IBS, abdominal pain.[30,31] Additional information regarding its use as a co-primary end point for IBS-D is included in the following section regarding the BSS.

Bristol Stool Scale for Stool Consistency

The BSS, also known as the Bristol Stool Form Scale, provides a standardized method for the classification of stool form, which is used as a surrogate measure of stool consistency.[24] There are a number of stool scales available, with the BSS being the most commonly used both clinically and in research. It is based on an ordinal scale from one to seven (hardest to softest), with types one and two suggesting constipation or abnormally hard stool, and types six and seven relating to loose/liquid stools, suggesting diarrhea.[24] Each of the seven types are described using both a written description and visual (pictorial) example.[24] Specifically:

- Type 1: Hard to pass, separate, nut-like, hard lumps
- Type 2: Lumpy, sausage-shaped
- Type 3: Like a sausage but with cracks on the surface
- Type 4: Like a sausage or snake, smooth and soft
- Type 5: Soft blobs with clear-cut edges (passed easily)

- Type 6: Fluffy pieces with ragged edges, a mushy stool
- Type 7: Entirely liquid. Watery, no solid pieces.

A recently published study validated the BSS in healthy patients and in patients with IBS-D.[24] Concurrent validity was evaluated two ways: by an assessment of the measured water content of real stools compared with classification by 169 lay participants and one of three experts; and by a comparison of the classification by healthy volunteers with that of the experts in gastrointestinal research. Based on the experts' categorization, only 36% of the healthy volunteers were correctly assigned, indicating a fair agreement (kappa = 0.25). A moderate correlation (Spearman's rho = 0.491) was reported for the evaluation of the comparison of measured water content–based rating to that of the healthy volunteers. Construct validity was also assessed by a comparison of a stool samples from 169 healthy volunteers and 19 patients with IBS-D. The mean rating based on participant-assigned BSS was significantly higher (softer/looser) for stool from patients with IBS-D compared with that of healthy volunteers.[24] The accuracy of the BSS was also evaluated using stool models, which demonstrated substantial overall accuracy (kappa = 0.78). Inter-rater reliability was assessed by having healthy volunteers classify duplicate stool models and comparing the classification, which revealed substantial intra-rater reliability (kappa = 0.72) corresponding to 76% of occasions of volunteers classifying the same stool type for duplicate models.[24] No assessment or measure of responsiveness of the BSS was found to determine the extent that the score can capture changes over time or with treatment.

Worst Abdominal Pain Score and Bristol Stool Scale as a Co-Primary End Point

Guidance from the European Medicines Agency (EMA) and FDA state that the ideal end point for use in clinical trials for IBS should be a multi-item, patient-reported outcome that is reflective of the clinically important signs and symptoms of IBS.[30,31] It should also have undergone rigorous validation, but no instrument designed for this purpose is currently available.[30,31] In place of the ideal end point, it is recommended that the primary end point used in clinical trials measure how treatment affects two of the major IBS signs and symptoms, which are abnormal defecation and abdominal pain.[30,31] For IBS-D specifically, the BSS and WAP scores are recommended as co-primary end points to serve this purpose.

Abdominal Bloating Score

The abdominal bloating score is a patient-reported outcome used to assess abdominal bloating based on a 24-hour recall. It is rated on an ordinal scale from 0 to 10, with a higher score corresponding to more severe bloating and 10 being equal to the worst imaginable bloating.[20,21] There was no evidence of validation identified for the abdominal bloating scale. However, the EMA suggested its use as a secondary end point to support the recommended primary end points for IBS, which are not fully validated.[30]

Abdominal Discomfort Score

The abdominal discomfort score is a patient-reported assessment of abdominal discomfort based on a 24-hour recall. It is rated on an ordinal scale from 0 to 10, with a higher score corresponding to more severe abdominal discomfort and 10 being the worst imaginable discomfort.[20,21] It is difficult to distinguish abdominal pain from abdominal discomfort in IBS patients, but the FDA and EMA suggest that pain and discomfort be treated separately.[30,31] Further, both agencies recommend that abdominal discomfort is used

as secondary end point for IBS-related trials and in support of the primary end points, as the abdominal discomfort score has not been validated.[30,31]

Irritable Bowel Syndrome with Predominant Diarrhea Global Symptom Score

The IBS-D global symptom score is a measurement of overall symptoms associated with IBS-D. It is a patient-reported outcome based on the previous 24 hours, and is assessed on a scale from 0 to 4, with 0 corresponding to no symptoms and 4 corresponding to very severe symptoms.[20,21] Scores of 2, 3, and 4 correspond to mild, moderate, and severe symptoms, respectively.[20,21] No evidence regarding the validity of the IBS-D global symptom score was identified. According to the EMA, a limitation of the global symptom score is that its use to assess improvement in patients with IBS may lead to an overestimation of the effect, as IBS is a multifaceted disease that is difficult to evaluate based on a single question.[30]Because it is not validated, it is recommended as a secondary end point in IBS-D clinical trials.[30,31]

34-item Irritable Bowel Syndrome Quality of Life Questionnaire

Living with IBS has been shown to have major impairments on health status and quality of life (QoL).[26] To evaluate the perceived QoL in patients with IBS, a disease-specific, 34-item questionnaire was developed. As the title suggests, it is a questionnaire consisting of 34 questions that are answered by patients according to a five-point Likert scale, with 1 corresponding to having the least impact on QoL, and 5 having the greatest impact.[26] The scale is rated as follows: 1 = “not at all,” 2 = “slightly,” 3 = “moderately,” 4 = “quite a bit,” and 5 = “extremely” or “a great deal.” The scores for the 34 items are summed to obtain a total IBS-QoL score. Moreover, the questionnaire can be divided into eight subscales, which were derived from a principal component factor analysis of the instrument, and include: dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual, and relationships.[26]

The IBS-QoL was constructed and validated in a study in the US that included patients who had IBS as per the Rome criteria diagnosis for IBS, had abdominal symptoms for at least two days each week, and were between the ages of 18 and 65.[26] This group included patients of all three subtypes, i.e., IBS-D, IBS with constipation (IBS-C) and IBS with mixed bowel habits (IBS-M), but they were not analyzed separately. Briefly, 117 items for the questionnaire were derived from interviews with 40 patients, and narrowed down to 45 through cognitive debriefing of a different group of 30 patients with IBS. Of the 45 items, 41 were deemed valid for adapted use in Britain, Germany, Italy, and France. Seven items were removed due to their ceiling effect or redundancy, leaving 34 items in the final version of the questionnaire, which was then administered to a group of 169 patients for validation, 156 (92%) of whom returned a completed questionnaire. The IBS-QoL was shown to have high internal consistency reliability, with a Cronbach’s alpha of 0.95 for the overall questionnaire, as well as a value of 0.74 to 0.92 for the subscales, with the exception of relationships (alpha = 0.65). The IBS-QoL also showed strong reproducibility, with an intraclass correlation coefficient (ICC) of 0.86 overall, and 0.76 to 0.89 for the subscales, except for relationships (ICC = 0.65). The IBS-QoL also demonstrated validity based on an assessment of construct validity and known-groups validity. The former was assessed through predicted correlations for the overall and subscale scores, all of which were confirmed with the exception of role physical, mental health, and vitality. Known-groups validity was evaluated by stratifying patients by mild, moderate, and high scores for

IBS frequency of symptoms and bothersome scores, where lower scores corresponded to an higher reported QoL.[26] An additional study by Andrae et al. validated the IBS-QoL in IBS-D patients specifically (n = 754), by replicating the initial validation process in patients enrolled in IBS-3001 and IBS-3002.[29] The IBS-QoL demonstrated reliability as per Cronbach's alpha = 0.963 (95% CI, 0.959 to 0.966), and estimated variances from a linear model (R_Λ and R_T of 0.89 and 0.76, respectively), which was used in lieu of an ICC. It also correlated with other measures of IBS-D symptoms and outcomes, including the FDA Clinical Responders and IBS-AR.

Another study by Drossman et al. sought out to determine the longitudinal construct validity or responsiveness of the IBS-QoL based on a sample of 156 female patients with functional bowel disorder (FBD) and enrolled in a 12-week trial for FBD treatment.[27] A statistically and clinically responsive change was observed in patients during the 12-week treatment period. Data from the same trial were later used to determine a minimal clinically important difference (MCID) for the IBS-QoL using anchor-based methods and a statistical approach using half of the standard deviation of the baseline values.[28] The following anchors were used to assess how the IBS-QoL correlates with clinical response: change in visual analogue score for pain and a treatment satisfaction questionnaire.[28] Change scores showed an improvement in the IBS-QoL score with the visual analogue score pain anchor and treatment satisfaction questionnaire anchor (13.81 ± 16.11 and 14.26 ± 16.46, respectively) that averaged out to 14, and which was also supported by the 1/2 standard deviation analyses. Thus, the authors suggested an MCID of 14 for the IBS-QoL.[28] A limitation of both studies is that a questionnaire designed specifically for IBS (the IBS-QoL) was used in a group of patients for whom it was not developed, i.e., those with FBD. However, 79% of the FBD patients reported having IBS. The subtype of IBS for those patients is also unknown. Further, the trial was limited to female patients, decreasing the generalizability of the validation results.

Adequate Relief of IBS Symptoms

The IBS-AR end point is a patient-reported, dichotomous, single-item outcome.[20,21] It is used to assess whether a patient has experienced adequate relief of IBS symptoms using the answer to the question, "Over the past week, have you had adequate relief of your IBS symptoms?"[14,20,21] There was no evidence of validity identified for the IBS-AR. Guidance on clinical evaluation of drugs for IBS from the FDA cites that the IBS-AR and similar single-item patient-reported outcomes were commonly used as a primary efficacy end point, although these outcomes do not provide useful information treatment effect on the severity of signs and/or symptoms.[31] For this reason, both the FDA and the EMA recommend that a multi-item patient-reported outcome be used as a primary end point for clinical trials instead of single-item end points such as the IBS-AR.[30,31]

Conclusion

A major concern with IBS-D is the impact on a patient's QoL. This increases the importance and relevance of patient-reported outcomes when evaluating treatments for IBS-D. Despite this fact, there is currently a lack of validated outcomes for the evaluation of treatments for IBS-D. At best, it has been recommended that an assessment of the two major signs and symptoms of IBS-D be included, which are abdominal pain and abnormal defecation.[30,31] The former is measured by the 11-point ordinal WAP score, although evidence of validation was not identified. Abnormal defecation for IBS-D patients can be measured using the BSS for stool consistency, as it is widely used in clinical and research settings and has undergone extensive validation.[24] The abdominal bloating score, abdominal discomfort score, IBS-D global symptom score, IBS-QoL, and IBS-AR were also reviewed. These outcomes have been suggested for use as secondary outcomes to support the co-primary outcomes, as no evidence of validation has been identified for any of these outcomes, with the exception of IBS-QoL. The IBS-QoL, developed in patients with all three subtypes of IBS, has been shown to exhibit measures of reliability, validity, and responsiveness that validate its use for IBS-D.[26-29] Further, a 14-point change was estimated as an MCID for the IBS-QoL, although this was based on data from a sample of female patients with FBD, including a diagnosis of IBS among 79% of patients.[28]

Appendix 5: Summary of Other Studies

Objective

To summarize the results of a phase II, proof-of-concept study (IBS-2001) that evaluated oral eluxadoline (Viberzi) in patients with Irritable bowel syndrome with predominant diarrhea (IBS-D) in terms of efficacy, safety, and health-related quality of life, with a focus on data from the EuroQol-5 Dimension 3-Levels questionnaire (EQ-5D-3L) to inform the corresponding CADTH Common Drug Review pharmacoeconomic report.

Findings

Study Design

The design characteristics of IBS-2001, a randomized, double-blind, placebo-controlled, phase II study, are summarized in Table 15. To be eligible for IBS-2001, patients needed to be between 18 and 65 years old, meet the Rome III criteria for IBS-D, and report both a mean daily worst abdominal pain (WAP) score of ≥ 3.0 and mean daily stool consistency score of ≥ 5.5 based on the Bristol stool scale (BSS), within the week preceding randomization. For the study, 807 patients were randomized in a 1:1:1:1:1 ratio to one of four intervention groups (5 mg, 25 mg, 100 mg, and 200 mg eluxadoline) or placebo. However, 18 patients were excluded from all datasets due to site termination for potential scientific misconduct, therefore the remaining 789 patients were used for the total number of patients randomized. The intervention involved the assigned dose of eluxadoline or placebo, taken twice daily with breakfast and dinner. In Canada, the Health Canada–approved dosages of eluxadoline are 75 mg and 100 mg of eluxadoline twice daily. Therefore, for the purposes of this summary, only the efficacy and safety results for the 100 mg eluxadoline arm and placebo will be reported.

The study was divided into four phases. First, a one-week prescreening phase involving a physical examination of patients, discontinuation of prohibited medications, and routine blood and urine testing was performed, followed by a two- to three-week screening phase during which eligible patients began to use an interactive voice response system (IVRS) to record daily symptom assessments. The double-blind trial phase began after the screening period and included patients who still met the eligibility criteria after screening, and were compliant with the IVRS system. The last phase was a two-week post-treatment period.

Table 15: Study Design and Characteristics of IBS-2001

		IBS-2001
Design and Populations	**Study design**	Randomized, double-blind, placebo-controlled, proof-of-concept
	Participants (N)	789[a]
	Eligibility	Patients aged 18 to 65 years who met the Rome III criteria for IBS-D, and reported the following in the week before randomization: a mean daily WAP score of ≥ 3.0 and mean daily stool consistency score of ≥ 5.5 on the BSS
	Primary objective	To evaluate the clinical response and safety of eluxadoline in patients with IBS-D
	Secondary objectives	To evaluate the treatment effect of eluxadoline compared with placebo based on pain, stool consistency, and frequency.
	Exploratory objectives	To evaluate the treatment effect of eluxadoline compared with placebo based on incontinence, urgency, and symptoms, and on patient-reported treatment outcomes.
Drugs	**Intervention**	5 mg, 25 mg, 100 mg, or 200 mg of eluxadoline, twice daily with breakfast and dinner
	Comparators	Placebo
Duration	**Prescreening**	• 1 week • Physical examination of patients, discontinuation of prohibited medications, and collection of blood and urine for routine testing
	Screening	• 2 to 3 weeks • Included patients who met the study inclusion/exclusion criteria • Patients began using IVRS to record daily symptom assessments • No rescue medication allowed
	Double-blind treatment	• 12 weeks • Included patients who still met the eligibility criteria after screening, 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 two weeks before • Limited rescue medication was permitted, with different rules for medication for diarrhea, pain, and constipation
	Post-treatment	• 2 weeks • Off-therapy bowel functioning and symptoms associated with IBS-D were assessed • Evaluation of post-treatment medication use
Outcomes	**Primary end point**	Clinical response during week 4, defined as a patient that exhibited: • a decrease of at least 30% from baseline in the mean daily WAP score and a decrease of at least 2 points; and • a score of 3 or 4 on the daily BSS for ≥ 66% of that week's daily diary entries
	Other end points	Secondary: • Percentage of patients who achieved clinical response at week 12; and • Percentage of patients who achieved response to the individual WAP and stool consistency components at weeks 4 and 12 Other secondary and exploratory: • EQ-5D-3L questionnaires

BSS = Bristol stool scale; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; IBS-D = Irritable bowel syndrome with diarrhea; IVRS = interactive voice response system; WAP = worst abdominal pain.

[a] Originally 807 patients were randomized; 18 patients were excluded from all datasets due to site termination for potential scientific misconduct.

Source: Clinical Study Report.[33]

Methods

The primary objective of IBS-2001 was to evaluate the clinical response and safety of eluxadoline in patients with IBS-D. Clinical response was defined as a co-primary end point at week 4 and composed of the following two outcomes: a mean daily WAP score decreased by ≥ 30% from baseline and at least two points; and a daily BSS score of 3 or 4 on ≥ 66% of daily diary entries during week 4. The secondary objective was to evaluate the treatment effect of eluxadoline compared with placebo based on pain (WAP, BSS), and frequency at weeks 4 and 12. The treatment effect of eluxadoline, based on incontinence, urgency, and symptoms, as well as patient-reported treatment outcomes, was also evaluated as an exploratory objective compared with placebo. For the purposes of this report, only the EQ-5D-3L data from the exploratory objective were included in this summary.

Patient Disposition

The patient disposition for IBS-2001 has been summarized in Table 16. A total of 1,802 patients underwent screening, 807 (44.8%) of whom were initially included and randomized for this study. Eighteen patients were excluded from all datasets due to site termination for potential scientific misconduct, therefore 789 patients (43.8%) were considered randomized participants. Of the 789 participants, 107 (13.6%), 173 (21.9%), 169 (21.4%), and 169 (21.7%) were randomized to the 5 mg, 25 mg, 100 mg, and 200 mg eluxadoline treatment groups, respectively, and 169 (21.4%) were assigned to placebo. A total of 520 (65.9%) patients completed the study, with completion rates ranging from 44.9% (5 mg treatment group) to 75.7% (25 mg treatment group). Further, 269 (34.1%) patients discontinued the study, with the most common reasons being sponsor decision (8.4%), adverse event or serious adverse event (5.3%), voluntary withdrawal (5.3%), and discontinuation of study arm (4.8%). Other reasons included use of rescue medication for diarrhea (3.8%), lost to follow-up (3.0%), protocol violation (1.6%), physician decision (0.6%), IVRS-confirmed constipation (0.5%), and lack of efficacy due to uncontrolled diarrhea (0.5%). Efficacy was assessed using a modified intention-to-treat set that included patients with at least one dose of study drug, baseline, and at least one assessment for pain and stool consistency after randomization.

Table 16: Patient Disposition for IBS-2001

Disposition, n (%)	Eluxadoline					
	5 mg	25 mg	100 mg	200 mg	Placebo	Total
Screening	NA	NA	NA	NA	NA	1,802
Double-blind treatment phase						
Enrolled	107 (100)	173 (100)	169 (100)	171 (100)	169 (100)	789 (100)
Completed	48 (44.9)	131 (75.7)	121 (71.6)	103 (60.2)	117 (69.6)	520 (65.9)
Discontinued	59 (55.1)	42 (24.3)	48 (28.4)	68 (39.8)	52 (30.8)	269 (34.1)
AE or SAE	2 (1.9)	5 (2.9)	6 (3.6)	22 (12.9)	7 (4.1)	42 (5.3)
Study arm discontinued	38 (35.5)	0	0	0	0	38 (4.8)
IVRS-confirmed constipation	0	1 (0.6)	1 (0.6)	2 (1.2)	0	4 (0.5)
Rescue medications due to diarrhea	3 (2.8)	5 (2.9)	8 (4.7)	8 (4.7)	6 (3.6)	30 (3.8)
Lack of efficacy due to uncontrolled diarrhea	1 (0.9)	1 (0.6)	0	0	2 (1.2)	4 (0.5)
Lack of efficacy due to uncontrolled IBS-D abdominal pain	0	0	0	1 (0.6)	0	1 (0.1)
LTFU	4 (3.7)	3 (1.7)	4 (2.4)	7 (4.1)	6 (3.6)	24 (3.0)
Protocol violation	0	0	3 (1.8)	5 (2.9)	5 (3.0)	13 (1.6)

Disposition, n (%)	Eluxadoline					
	5 mg	25 mg	100 mg	200 mg	Placebo	Total
Voluntary withdrawal	4 (3.7)	11 (6.4)	10 (5.9)	9 (5.3)	8 (4.7)	42 (5.3)
Physician decision	1 (0.9)	1 (0.6)	0	1 (0.6)	2 (1.2)	5 (0.6)
Sponsor decision	6 (5.6)	15 (8.7)	19 (9.5)	13 (7.6)	16 (9.5)	66 (8.4)
Randomized/full analysis set	107 (100)	173 (100)	169 (100)	171 (100)	169 (100)	789 (100)
mITT set	105 (98.1)	167 (96.5)	163 (96.4)	160 (93.6)	159 (94.1)	754 (95.6)

AE = adverse event; mITT = modified intention to treat; IVRS = interactive voice response system; LTFU = lost to follow-up; SAE = serious adverse event.

Note: Discontinuation data are based on the primary reason for discontinuation.

Source: Clinical Study Report.[33]

Baseline Characteristics

The baseline characteristics for the phase II study are summarized in Table 17. Patients had a mean age of 44.8 (standard deviation [SD] 11.9), and the majority were female (70%), and white (85.7%). The mean body mass index was 30.7 (SD 7.6) based on data from 752 patients (99.7%). In brief, the IBS characteristics were fairly similar across treatment groups, with a mean WAP score of 5.9 (SD 1.63), bowel movement frequency of 4.8 (SD 3.28), stool consistency score of 6.2 (SD 0.43), number of urgency episodes of 3.3 (SD 2.83), and number of incontinence episodes of 1.0 (SD 2.02).

Table 17: Baseline Demographic and IBS Characteristics (mITT Set)

Characteristic	Eluxadoline					
	5 mg (N = 105)	25 mg (N= 167)	100 mg (N = 163)	200 mg (N = 160)	Placebo (N = 159)	Total (N = 754)
Demographics						
Age, mean (SD)	45.5 (12.9)	45.6 (11.9)	43.6 (10.9)	44.8 (11.7)	44.6 (12.5)	44.8 (11.9)
Sex, n (%)						
Male	31 (30)	51 (31)	50 (31)	47 (29)	49 (31)	228 (30)
Female	74 (70)	116 (69)	113 (69)	113 (71)	110 (69)	526 (70)
Race, n (%)						
White	88 (83.8)	139 (83.2)	140 (85.9)	137 (85.6)	142 (89.3)	646 (85.7)
Black or African American	12 (11.4)	20 (12.0)	17 (10.4)	17 (10.6)	15 (9.4)	81 (10.7)
Asian	3 (2.9)	4 (2.4)	3 (1.8)	4 (2.5)	2 (1.3)	16 (2.1)
American Indian or Alaska Native	1 (1.0)	2 (1.2)	0	0	0	3 (0.4)
Other	1 (1.0)	2 (1.2)	3 (1.8)	2 (1.3)	0	8 (1.1)
BMI						
n (%)	105 (100)	167 (100)	163 (100)	159 (99.4)	158 (99.4)	752 (99.7)
mean (SD)	31.9 (7.8)	30.5 (8.5)	30.3 (7.1)	30.7 (7.4)	30.7 (7.2)	30.7 (7.6)
IBS characteristics, mean (SD)						
Pain	5.8 (1.54)	5.9 (1.70)	6.1 (1.72)	5.8 (1.48)	5.9 (1.67)	5.9 (1.63)
Stool consistency	6.2 (0.45)	6.2 (0.40)	6.2 (0.43)	6.2 (0.42)	6.2 (0.44)	6.2 (0.43)
BM frequency	4.6 (2.47)	4.4 (3.16)	5.1 (3.59)	5.0 (3.21)	4.9 (3.57)	4.8 (3.28)
Urgency episodes	3.1 (1.96)	3.0 (2.92)	3.5 (3.32)	3.3 (2.33)	3.3 (3.15)	3.3 (2.83)
Incontinence episodes	1.1 (1.64)	0.9 (1.95)	1.1 (2.20)	0.9 (1.35)	1.1 (2.63)	1.0 (2.02)

BM = bowel movement; BMI = body mass index; IBS = Irritable bowel syndrome; mITT = modified intention to treat; SD = standard deviation.

Source: Clinical Study Report.[33]

Results

Efficacy

A summary of the clinical response to treatment at week 4 is outlined in Table 18. Based on the composite end point, 11.0% of patients receiving eluxadoline achieved clinical response at week 4, compared with 5.7% in the placebo group, which corresponds to an odds ratio (OR) of 2.08 (95% CI, 0.89 to 4.84). The percentage of clinical responders for abdominal pain was similar in both patients receiving eluxadoline and placebo (39.3% and 39.6%, respectively), with no statistical significance observed between the treatment group and placebo. As for stool consistency, the percentage of responders was greater in the treatment group (14.1%) than in placebo (8.2%), corresponding to an OR of 1.90 (95% CI, 0.92 to 3.92).

Table 18: Primary Efficacy Results: Clinical Response Criteria (mITT Set)

	100 mg Eluxadoline (N = 163)	Placebo (N = 159)
Clinical Response, Week 4		
Composite, % responders	11.0	5.7
OR (95% CI), *P* value	2.08 (0.89 to 4.84), *P* = 0.090	NA
Abdominal pain, % responders	39.3	39.6
OR (95% CI), *P* value	0.99 (0.62 to 1.60), *P* = 0.974	NA
Stool consistency, % responders	14.1	8.2
OR (95% CI), *P* value	1.90 (0.92 to 3.92), *P* = 0.083	NA

CI = confidence interval; mITT = modified intention to treat; OR = odds ratio.

Source: Clinical Study Report.[33]

The clinical response to treatment at week 12 data is summarized in Table 19.
A statistically significant ($P < 0.05$) percentage of patients were clinical responders in the 100 mg treatment group, compared with placebo (11.3%), with an OR of 2.01 (95% CI, 1.07 to 3.80). The percentage of clinical responders by abdominal pain was 49.1% in the 100 mg group compared with 39.6% in the placebo group, which was a statistically significant difference ($P < 0.05$). The OR corresponding to the abdominal pain measure in the treatment group and placebo group was 1.49 (95% CI, 0.94 to 2.34). A statistically significant difference was also reported for stool consistency, with 22.1% of patients in 100 mg treatment group achieving clinical response compared with 15.1% of patients in the placebo group, which corresponded to an OR of 1.64 (95% CI, 0.91 to −2.94).

Table 19: Secondary Efficacy Results: Clinical Response Criteria (mITT Set)

	100 mg Eluxadoline (N = 163)	Placebo (N = 159)
Clinical response, Week 12		
Composite, % responders	20.2	11.3
OR (95% CI), *P* value	2.01 (1.07 to −3.80), *P* = 0.030	NA
Abdominal pain, % responders	49.1	39.6
OR (95% CI), *P* value	1.49 (0.94 to −2.34), *P* = 0.087	NA
Stool consistency, % responders	22.1	15.1
OR (95% CI), *P* value	1.64 (0.91 to −2.94), *P* = 0.098	NA

CI = confidence interval; ; mITT = modified intention to treat; OR = odds ratio.

Source: Clinical Study Report.[33]

The health-related quality-of-life data obtained for this study via the EQ-5D-3L has been summarized in Table 20. The adjusted mean change from baseline and standard error (SE) at week four was 0.06 (0.01) in both the treatment group and placebo group. At week 12, the EQ-5D-3L results were greater in the 100 mg group (0.11, SE 0.01) compared with placebo (0.05, SE 0.01), with a statistically significant difference between the two ($P < 0.05$).

Table 20: Exploratory Outcomes of Interest: EQ-5D-3L Results (mITT Set)

	100 mg Eluxadoline (N = 163)	Placebo (N = 159)
Week 4		
n (%)	137 (84)	135 (85)
Adjusted mean change from baseline (SE)	0.06 (0.01)	0.06 (0.01)
Mean difference (SE) versus placebo	−0.003 (0.02)	NA
95% CI	−0.04, 0.03	NA
Week 12		
n (%)	152 (93)	146 (92)
Adjusted mean change from baseline (SE)	0.11 (0.01)	0.07 (0.01)
Mean difference (SE) versus placebo	0.05 (0.02)[a]	NA
95% CI	0.01, 0.09	NA

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; mITT = modified intention to treat; SE = standard error.

[a] $P < 0.05$.

Source: Clinical Study Report, p. 407.[33]

Limitations

There are several limitations to consider in the analysis of this phase II study for eluxadoline in patients with IBS-D. The WAP score and the BSS for stool consistency were used in combination as part of the inclusion/exclusion criteria, the primary end point, and secondary end point. The WAP score is a subjective, patient-reported outcome for which evidence of validity has not been identified. In addition, the primary and secondary end points of this study rely on scores obtained in the previous week, corresponding to the week of interest (i.e., weeks 4 and 12), as opposed to measuring these outcomes every week or more frequently. These analysis time points do not account for day-to-day variation of symptoms that are characteristic of patients with IBS-D. Further, the results for abdominal pain as measured by the WAP score were very similar, and also used as a co-primary end point with the BSS, which may skew the results of the composite score. Regarding the analysis plan, efficacy was evaluated using a modified intention-to-treat approach, which excluded some patients from the analysis. Sensitivity analyses and accounting for missing data using the baseline observation carried forward imputation method were used. However, the overall discontinuation rate was 34.1%, which leads to considerable uncertainty in the data. In addition, adjustments for multiple comparisons were not performed for the any of the analyses in this study, thus introducing a risk of type I error.

Summary

The phase II trial of eluxadoline for patients with IBS-D showed benefit in terms of efficacy when compared with placebo. This is based on the primary composite end point, which takes into account abdominal pain and stool consistency, two major symptoms of IBS-D, after four weeks. Continued benefit was observed at week 12, based on the same composite end point and in comparison with placebo. Interpretation of the efficacy results are limited by the use of a composite end point that utilizes a non-validated outcome, the WAP score, which is also a subjective, patient-reported outcome and therefore subject to bias. The risk of type I error must also be considered as adjustments for multiple comparisons were not performed in this study.

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