Common Drug Review
Clinical Review Report

September 2015

Drug	linaclotide (Constella)
Indication	For the treatment of irritable bowel syndrome with constipation (IBS-C) in adults.
Listing request	For treatment of IBS-C in adults.
Manufacturer	Actavis Specialty Pharmaceuticals Co

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

AE	adverse event
APC	abdominal pain and complete spontaneous bowel movement
APC +1 6/12	patients who had an abdominal pain response with an improvement of ≥ 1 complete spontaneous bowel movement (CSBM) over baseline per week in six of 12 weeks
APC 3+1 9/12	patients who had an abdominal pain response and at least three CSBMs and an improvement of ≥ 1 CSBM over baseline per week in nine of 12 weeks
BM	bowel movement
BSFS	Bristol Stool Form Scale
CDR	CADTH Common Drug Review
cGMP	cyclic guanosine monophosphate
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CSBM	complete spontaneous bowel movement
CSBM 3+1 9/12	patients who had at least three CSBMs and an improvement of ≥ 1 CSBM over baseline per week, for at least nine of 12 weeks
DB	double-blind
EOT	end of trial
EQ-5D	EuroQol 5-Dimensions Questionnaire
FDA	Food and Drug Administration
GI	gastrointestinal
HRUQ	Health Resource Use Questionnaire
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with constipation
IBS-QOL	Irritable Bowel Syndrome Quality of Life measure
ITT	intention-to-treat
IVRS	interactive voice response system
LS	least squares
MCID	minimal clinically important difference
NA	not applicable
PRCQ	patient rating of change questions
RCT	randomized controlled trial
RW	randomized withdrawal
SBM	spontaneous bowel movement
SD	standard deviation
SE	standard error
SSRI	selective serotonin reuptake inhibitor
WPAI:IBS-C	Work Productivity and Activity Impairment Questionnaire: Irritable Bowel Syndrome with Constipation Predominant Symptoms

EXECUTIVE SUMMARY

Introduction

Irritable bowel syndrome (IBS) is a common disorder of the gastrointestinal tract characterized by symptoms of abdominal pain and altered bowel habits that affect the frequency and consistency of bowel movements. Patients with IBS can either suffer from constipation (IBS-C) or diarrhea (IBS-D) or mixed IBS (IBS-M). The strict definition of IBS is recurrent abdominal pain or discomfort at least three days per month in the past three months with two or more of: improvement with defecation, onset associated with a change in frequency of stool, or onset associated with a change in appearance of stool. IBS-D is defined as presence of loose watery stools with at least 25% of bowel movements and hard or lumpy stools with less than 25% of bowel movements, while IBS-C is defined as the reverse — hard or lumpy stools with at least 25% of bowel movements and loose or watery stools with less than 25% of bowel movements.[1,2]

Initial management strategies for patients with mild to moderate symptoms include dietary modifications such as removal of gas-producing foods from the diet, assessment for lactose intolerance and food allergies, avoidance of gluten, and avoidance of foods that contain fermentable saccharides and polyols. Among interventions, fibre, in the form of psyllium, provides overall symptom relief of IBS, although this recommendation is weak according to the American College of Gastroenterology (ACG).[2] Insoluble fibre may exacerbate symptoms such as bloating. Antispasmodics also received a weak recommendation from the ACG, as did antidepressants. With respect to antispasmodics, anticholinergic side effects were seen as a limitation to their use, and the quality of evidence was considered to be low due to a number of older trials. Recommended antidepressants included the selective serotonin reuptake inhibitors (SSRIs) and tricyclics; however, adverse effects were also considered to be a limitation of these drugs, and a specific example of the constipating effects of tricyclics was given.[1,2]

Linaclotide is an orally administered guanylate cyclase-C (GC-C) agonist. Stimulation of intestinal GC-C leads to increased cyclic guanosine monophosphate (cGMP), which stimulates the cystic fibrosis transmembrane receptor (CFTR) ion channel. This leads to increased secretion of chloride and bicarbonate into the lumen and peristalsis within the gastrointestinal tract. Additionally, through stimulation of cGMP, linaclotide may also reduce intestinal pain by inhibiting nerve conduction.[3]

Linaclotide is indicated for the treatment of IBS-C in adults, and is administered at a dose of 290 mcg once daily.

Indication under review
For the treatment of irritable bowel syndrome with constipation (IBS-C) in adults.
Listing criteria requested by sponsor
For the treatment of IBS-C in adults.

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

Results and Interpretation

Included Studies

Two multi-centre, manufacturer-sponsored, pivotal, phase 3, double-blind (DB), randomized controlled trials (RCTs) — study MD-31 and study 302 — met the inclusion criteria for this review. Both studies were North American, although only MD-31 had Canadian sites. In both studies, approximately 800 patients with IBS-C exhibiting both abdominal pain and bowel symptoms were randomized 1:1 to either linaclotide or placebo; it was not reported whether randomization was stratified. The length of the placebo-controlled treatment period differed between studies, with a 12-week period in MD-31 and a 26-week treatment period in study 302. However, the primary outcomes in both studies were assessed at 12 weeks. Both studies had the same four primary outcomes, and response for each outcome was assessed weekly. One primary outcome focused on the proportion of patients who achieved a certain threshold of improvement in abdominal pain, while another focused on improvement in bowel symptoms, assessing the proportion of patients who had at least three complete spontaneous bowel movements (CSBMs) and improvement of ≥ 1 CSBM over baseline (CSBM 3+1) response per week. For each of these outcomes, patients were counted as "responders" if they had weekly responses in at least nine of 12 weeks (CSBM 3+1 9/12) responders. The other two primary outcomes assessed a combination of abdominal pain and bowel symptoms, reporting on the proportion of patients who had an abdominal pain response and a CSBM 3+1 response in nine of 12 weeks (APC 3+1 9/12) responders, and the proportion of abdominal pain responders with an improvement of ≥ 1 CSBM over baseline in six of 12 weeks (APC +1 6/12) responders. The final primary outcome was recommended for usage by the FDA.

Key critical appraisal points include the relatively high rate of discontinuations in both studies, and the higher discontinuation rate with linaclotide (23%) versus placebo (16%) in MD-31. The nature of the analysis conducted, which relied on weekly assessment of CSBM and of abdominal pain in order to determine overall response, may have been impacted by a high withdrawal rate and a differential rate of withdrawals. Additionally, blinding may have been somewhat compromised given the higher proportion of patients in the linaclotide groups experiencing diarrhea and the fact that patients would likely anticipate the study drug to cause this adverse effect. Key factors influencing external validity include the lack of an active comparator, and the fact that quality of life, a key efficacy outcome in IBS-C, was assessed only as an exploratory outcome and not included in the statistical testing hierarchy that controlled for multiplicity. There is uncertainty regarding how the data were handled for patients lost to follow-up, which may impact the reported rates of responders. Low rates of concurrent medications that have an impact on disease course suggest alternative therapies may not have been optimized in the trial before starting linaclotide. Both trials screened out a large number of patients and had strict enrolment criteria, limiting generalizability to the general population.

Efficacy

Overall response rates as measured by the primary outcomes in both studies were low. In MD-31, the proportion of CSBM 3+1 9/12 responders was 20% among linaclotide-treated patients and 6% among placebo-treated patients, and this difference was statistically significant between groups (odds ratio 3.7 [95% confidence interval (CI), 2.3 to 5.9]; $P < 0.0001$). In study 302, the proportion of CSBM 3+1 9/12 responders was 18% with linaclotide and 5% with placebo, and this difference between groups was also statistically significant (odds ratio 4.2 [95% CI, 2.5 to 7.0]; $P < 0.0001$).

Mean CSBM frequency was reported on a weekly basis, and there was an increase from baseline in the weekly least squares (LS) mean (± standard error [SE]) CSBM in both the linaclotide (2.27 ± 0.13) and placebo (0.71 ± 0.13) groups in study MD-31. The LS mean difference between groups was 1.57 (95% CI,

1.24 to 1.90), *P* < 0.0001. In study 302, the increase in weekly LS mean (SE) CSBM was 2.24 (0.12) with linaclotide and 0.70 (0.12) with placebo, and the LS mean difference between groups was also statistically significant (1.54 [95% CI, 1.23 to 1.85], *P* < 0.0001). These differences appear to be clinically significant, based on the reported minimal clinically important difference (MCID) for IBS-C of 1.3 to 1.5.

In study MD-31, there was an increase from baseline in weekly spontaneous bowel movement (SBM) rate in both the linaclotide (LS mean ± SE) (3.90 ± 0.18) and placebo (1.13 ± 0.18) groups, and the difference between groups was statistically significant (LS mean difference 2.77 [95% CI, 2.32 to 3.22]; *P* < 0.0001). In study 302, increases (LS ± SE) in weekly SBM rate were seen in both the linaclotide (4.02 ± 0.18) and placebo (1.31 ± 0.18) groups, and the difference between groups was statistically significant (LS mean difference 2.70 [95% CI, 2.26 to 3.15]; *P* < 0.0001). Based on the MCID for SBM of 1.9, these differences appear to be clinically significant.

Abdominal pain responders were patients who had achieved ≥ 30% improvement in their abdominal pain in at least nine of the 12 weeks of the study. In MD-31, 34% of linaclotide patients and 27% of placebo patients were abdominal pain responders, and the difference between groups was statistically significant (odds ratio 1.4 [95% CI, 1.0 to 1.9]; *P* = 0.0262). In study 302, the proportion of abdominal pain responders was 39% with linaclotide and 20% with placebo, and this difference between groups was also statistically significant (odds ratio 2.6 [95% CI, 1.9 to 3.6]; *P* < 0.0001). Abdominal pain was also expressed as a mean change from baseline in weekly abdominal pain scores after 12 weeks, with a LS mean (SE) change from baseline of –1.87 (0.09) with linaclotide and –1.13 (0.09) with placebo, for a LS mean difference of –0.74 (95% CI, –0.98 to –0.50); *P* < 0.0001 in study MD-31. Study 302 had a LS mean (SE) of –1.85 (0.09) with linaclotide and –1.07 (0.09) with placebo, for a LS mean difference of –0.78 (95% CI, –1.02 to –0.55); *P* < 0.0001.

Abdominal discomfort was also reported in both studies. After 12 weeks, the LS mean ± SE change from baseline in weekly abdominal discomfort score in study MD-31 was –1.95 ± 0.10 with linaclotide and –1.21 ± 0.10 with placebo, and the difference was statistically significant with a LS mean difference of –0.74 (95% CI, –0.99 to –0.49); *P* < 0.0001. In study 302, the LS mean ± SE change from baseline with linaclotide was –1.94 ± 0.00 and with placebo was –1.10 ± 0.09, and the difference between groups was also statistically significant, with a LS mean difference of –0.84 (95% CI, –1.07 to –0.60); *P* < 0.0001.

Bloating was also reported in both studies. After 12 weeks, the LS mean ± SE change from baseline in weekly abdominal bloating scores in study MD-31 was –1.94 ± 0.10 with linaclotide and –1.10 ± 0.10 with placebo, and the difference between groups was statistically significant with a LS mean difference of –0.84 (95% CI, –1.10 to –0.59); *P* < 0.0001. In study 302, the LS mean ± SE change from baseline with linaclotide was –1.91 ± 0.09 and with placebo was –1.03 ± 0.10, and this difference between groups was statistically significant, with a LS mean difference of –0.88 (95% CI, –1.12 to –0.64); *P* < 0.0001.

In study MD-31, after 12 weeks the LS mean ± SE change from baseline in weekly stool consistency scores was 2.07 ± 0.06 with linaclotide and 0.66 ± 0.06 with placebo, and the difference between groups was statistically significant, with a LS mean difference of 1.41 (95% CI, 1.25 to 1.57); *P* < 0.0001. In study 302, the LS mean ± SE with linaclotide was 1.91 ± 0.06 and with placebo was 0.61 ± 0.06, and this difference between groups was statistically significant, with a LS mean difference of 1.31 (95% CI, 1.15 to 1.47); *P* < 0.0001.

Straining was reported in both trials. In study MD-31, after 12 weeks the LS mean ± SE change from baseline in weekly straining scores –1.31 ± 0.04 with linaclotide and –0.65 ± 0.04 with placebo, and the

difference between groups was statistically significant, with a LS mean difference of –0.66 (95% CI, –0.76 to –0.55); *P* < 0.0001. In study 302, the LS mean ± SE with linaclotide was –1.24 ± 0.04 and with placebo was –0.66 ± 0.05, and this difference between groups was statistically significant, with a LS mean difference of –0.57 (95% CI, –0.69 to –0.46); *P* < 0.0001. Based on the reported MCIDs, it is not clear whether these differences for stool consistency and straining are clinically significant.

Quality of life was assessed as an exploratory outcome with no adjustment for multiple comparisons. Therefore these data must be interpreted with caution. [redacted] However, with no adjustment made for multiplicity, the risk of inflated type 1 error was not controlled, increasing the chances of finding a statistically significant difference when no true difference exists. As well, the observed difference between groups seen does not achieve MCIDs established in similar populations to those studied.

Quality of life was also assessed using the EuroQol 5-Dimensions Questionnaire (EQ-5D), once again as an exploratory outcome. No statistical analyses were provided. [redacted]

Hospitalizations were reported as part of a health resource utilization questionnaire but this was an exploratory outcome and no statistical analysis was planned. Absenteeism and other measures of work productivity were assessed using the Work Productivity and Activity Impairment Questionnaire: Irritable Bowel Syndrome with Constipation Predominant Symptoms (WPAI:IBS-C), although this was an exploratory outcome and no statistical analyses were performed.

Harms

Adverse events were reported after 12 weeks of therapy in MD-31, in which there were 56% of linaclotide patients and 53% of placebo patients with an adverse event. In study 302, after 26 weeks of therapy, 65% of linaclotide patients and 57% of placebo patients reported an adverse event. The most common adverse event was diarrhea in both studies, occurring in 20% of linaclotide patients and 4% of placebo patients in study MD-31 and 20% of linaclotide patients and 3% of placebo patients in study 302.

Serious adverse events were reported in 1% of patients after 12 weeks in each of the linaclotide and placebo groups in study MD-31, and in 1% of linaclotide patients and 2% of placebo patients in study 302 after 26 weeks.

Withdrawals due to adverse events occurred in 8% of linaclotide patients and 3% of placebo patients after 12 weeks in study MD-31, and in 10% of linaclotide patients and 3% of placebo patients after 26 weeks in study 302. The most common AE leading to withdrawal was diarrhea in both studies, in study MD-31 occurring in 6% of linaclotide patients and < 1% of placebo patients, and in study 302 in 5% of linaclotide patients and < 1% of placebo patients.

Notable harms were gastrointestinal, the most common of which was diarrhea, as reported above. Other gastrointestinal adverse events included abdominal pain — occurring in 5% of linaclotide patients and 3% of placebo patients after 12 weeks in MD-31, and in 5% of linaclotide patients and 4% of placebo patients in study 302 — and flatulence, occurring in 5% of linaclotide patients and 2% of placebo patients in MD-31, and in 4% of linaclotide patients and 2% of placebo patients in study 302. Infectious diseases of the gastrointestinal tract were also a notable harm, and viral gastroenteritis occurred in [redacted] 4% of linaclotide patients and 2% of placebo patients in study 302.

In the extension trials, patients who were initially excluded from randomization who eventually received linaclotide experienced higher rates of adverse effects, driven by the rate of diarrhea, than those included in the two RCTs. This suggests that tolerability outside of the highly selected population in the RCTs may be worse than that observed in the trials.

Conclusions

Two multicentre, manufacturer-sponsored, placebo-controlled, DB RCTs — study MD-31 and study 302 — met the inclusion criteria for this review. The studies each enrolled approximately 800 patients with IBS-C, exhibiting both symptoms of constipation and abdominal pain, and randomized them 1:1 to either linaclotide or placebo. Study MD-31 compared linaclotide with placebo over a 12-week treatment period, while study 302 compared linaclotide with placebo over a 26-week treatment period. Both studies had four primary outcomes assessed at 12 weeks: proportion of responders with respect to abdominal pain, complete spontaneous bowel movements, and two composites that combined abdominal pain and improvement in complete spontaneous bowel movements. Linaclotide was associated with statistically superior improvements in each of the four primary outcomes in both studies. Several other measures of abdominal and bowel symptoms were also reported as secondary outcomes, and these were all statistically significantly improved versus placebo. Quality of life was assessed only as an exploratory outcome, therefore although statistically, but not clinically, significant improvements for linaclotide over placebo were reported on a disease-specific instrument, these findings must be considered hypothesis-generating. Given that overall response rates to the primary outcomes were low in a highly selective population, balanced with high withdrawal rates and high observed rates of adverse effects and low usage of concurrent therapies, the clinical benefit of linaclotide in the general population is uncertain.

TABLE 1: SUMMARY OF RESULTS

	MD-31		Study 302	
APC 3+1 Responder, 9/12 Weeks	**Linaclotide (N = 405)**	**Placebo (N = 395)**	**Linaclotide (N = 401)**	**Placebo (N = 403)**
N (%)	49 (12)	20 (5)	51 (13)	12 (3)
OR (95% CI)	2.60 (1.51 to 4.47)		4.65 (2.44 to 8.84)	
P value	*P* = 0.0004[a]		*P* < 0.0001[a]	
CSBM 3+1 Responder, 9/12 Weeks				
N (%)	79 (20)	25 (6)	72 (18)	20 (5)
OR (95% CI)	3.65 (2.26 to 5.88)		4.19 (2.50 to 7.03)	
P value	*P* < 0.0001[a]		*P* < 0.0001[a]	
Abdominal Pain Responder, 9/12 Weeks				
N (%)	139 (34)	107 (27)	156 (39)	79 (20)
OR (95% CI)	1.41 (1.04 to 1.91)		2.62 (1.91 to 3.60)	
P value	*P* = 0.0262[a]		*P* < 0.0001[a]	
APC +1 Responder, 6/12 Weeks				
N (%)	136 (34)	83 (21)	135 (34)	56 (14)
OR (95% CI)	1.93 (1.40 to 2.66)		3.16 (2.22 to 4.49)	
P value	*P* < 0.0001[a]		*P* < 0.0001[a]	
12-Week CSBM Frequency Rate				
Mean (SD) baseline	0.203 (0.457)	0.238 (0.505)	0.176 (0.404)	0.213 (0.446)
Mean (SD), weeks 1 to 12	2.568 (3.088)	1.040 (1.413)	2.374 (2.949)	0.884 (1.412)
LS mean change from baseline (SE)	2.272 (0.127)	0.705 (0.128)	2.239 (0.122)	0.699 (0.122)
LS MD (95% CI)	1.568 (1.241 to 1.895)		1.540 (1.230 to 1.850)	
P value	*P* < 0.0001[b]		*P* < 0.0001[b]	
12-Week SBM Frequency Rate				
Mean (SD) baseline	1.935 (1.378)	1.897 (1.399)	1.745 (1.363)	1.739 (1.367)
Mean (SD), weeks 1 to 12	5.977 (4.382)	3.174 (2.222)	5.701 (4.225)	2.987 (2.467)
LS mean change from baseline (SE)	3.898 (0.176)	1.130 (0.177)	4.017 (0.176)	1.313 (0.176)
LS MD (95% CI)	2.769 (2.315 to 3.223)		2.704 (2.255 to 3.153)	
P value	*P* < 0.0001[b]		*P* < 0.0001[b]	
12-Week Stool Consistency				
Mean (SD) baseline	2.260 (0.994)	2.395 (1.026)	2.381 (1.080)	2.293 (0.961)
Mean (SD), weeks 1 to 12	4.454 (1.238)	3.088 (0.955)	4.314 (1.303)	2.976 (0.921)
LS mean change from baseline (SE)	2.071 (0.060)	0.662 (0.061)	1.914 (0.063)	0.607 (0.064)
LS MD (95% CI)	1.409 (1.253 to 1.565)		1.307 (1.146 to 1.468)	
P value	*P* < 0.0001[b]		*P* < 0.0001[b]	
12-Week Severity of Straining				
Mean (SD) baseline	3.579 (0.756)	3.449 (0.790)	3.570 (0.817)	3.545 (0.782)
Mean (SD), weeks 1 to 12	2.164 (0.797)	2.779 (0.747)	2.295 (0.842)	2.854 (0.782)

	MD-31		Study 302	
APC 3+1 Responder, 9/12 Weeks	**Linaclotide (N = 405)**	**Placebo (N = 395)**	**Linaclotide (N = 401)**	**Placebo (N = 403)**
LS mean change from baseline (SE)	–1.306 (0.042)	–0.651 (0.042)	−1.235 (0.044)	−0.663 (0.045)
LS MD (95% CI)	–0.655 (–0.763 to –0.546)		−0.572 (−0.686 to −0.459)	
P value	*P* < 0.0001[b]		*P* < 0.0001[b]	
12-Week Abdominal Pain				
Mean (SD) baseline	5.656 (1.648)	5.633 (1.707)	5.628 (1.738)	5.535 (1.726)
Mean (SD), weeks 1 to 12	3.653 (2.134)	4.377 (2.194)	3.683 (2.114)	4.397 (2.054)
LS mean change from baseline (SE)	–1.869 (0.093)	–1.129 (0.094)	−1.852 (0.093)	−1.070 (0.093)
LS MD (95% CI)	–0.740 (–0.981 to –0.499)		−0.782 (−1.019 to −0.545)	
P value	*P* < 0.0001[b]		*P* < 0.0001[b]	
12-Week Abdominal Discomfort				
Mean (SD) baseline	6.170 (1.600)	6.041 (1.672)	6.124 (1.699)	5.980 (1.690)
Mean (SD), weeks 1 to 12	4.070 (2.146)	4.721 (2.145)	4.116 (2.094)	4.851 (1.993)
LS mean change from baseline (SE)	–1.953 (0.096)	–1.211 (0.097)	-1.940 (0.002)	-1.103 (0.092)
LS MD (95% CI)	–0.742 (–0.990 to –0.494)		−0.837 (−1.071 to −0.603)	
P value	*P* < 0.0001[b]		*P* < 0.0001[b]	
12-Week Bloating				
Mean (SD) baseline	6.712 (1.771)	6.496 (1.890)	6.650 (1.874)	6.494 (1.819)
Mean (SD), weeks 1 to 12	4.623 (2.335)	5.306 (2.276)	4.681 (2.239)	5.445 (2.141)
LS mean change from baseline (SE)	–1.944 (0.099)	–1.100 (0.100)	−1.914 (0.094)	−1.032 (0.095)
LS MD (95% CI)	–0.844 (–1.101 to –0.587)		−0.882 (−1.123 to −0.641)	
P value	*P* < 0.0001[b]		*P* < 0.0001[b]	
IBS-QOL Overall Score				
Mean (SD) baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change, baseline to end point	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	
EQ-5D Index				
Mean (SD) baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change, baseline to end point	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D VAS				
Mean (SD) baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change, baseline to end point	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Events				
Patients with > 0 AEs, N (%)	228 (56)	210 (53)	263 (65)	228 (57)
Serious Adverse Events				
Patients with > 0 SAEs, N (%)	2 (1)	2 (1)	4 (1)	7 (2)

	MD-31		Study 302	
APC 3+1 Responder, 9/12 Weeks	**Linaclotide (N = 405)**	**Placebo (N = 395)**	**Linaclotide (N = 401)**	**Placebo (N = 403)**
WDAEs				
WDAEs, N (%)	32 (8)	11 (3)	41 (10)	10 (2)
Deaths				
Number of deaths, N (%)	0	0	0	0
Notable Harms				
Diarrhea	79 (20)	14 (4)	79 (20)	10 (3)
Abdominal pain	22 (5)	10 (3)	18 (5)	16 (4)
Flatulence	20 (5)	6 (2)	15 (4)	9 (2)
Viral gastroenteritis	[redacted]	[redacted]	15 (4)	9 (2)

AE = adverse event; APC = abdominal pain and complete spontaneous bowel movement; APC +1 responder, 6/12 weeks = a patient who had an abdominal pain response with an improvement of ≥ 1 complete spontaneous bowel movement (CSBM) over baseline per week in six of 12 weeks; APC 3+1 responder, 9/12 weeks = a patient who had an abdominal pain response and at least three CSBMs and an improvement of ≥ 1 CSBM over baseline per week in nine of 12 weeks; CI = confidence interval; CSBM = complete spontaneous bowel movement; CSBM 3+1 responder, 9/12 weeks = a patient who had at least three CSBMs and an improvement of ≥ 1 CSBM over baseline per week in nine of 12 weeks; EQ-5D = EuroQol 5-Dimensions Questionnaire; IBS-QOL = Irritable Bowel Syndrome Quality of Life measure; LS = least squares; MD = mean difference; OR = odds ratio; SAE = serious adverse event; SBM = spontaneous bowel movement; SD = standard deviation; SE = standard error; VAS = visual analogue scale; WDAE = withdrawal due to adverse event.

[a] *P* values and odds ratio based on the Cochran–Mantel–Haenszel (CMH) test controlling for geographic region.

[b] *P* values are based on a comparison of linaclotide versus placebo in an analysis of covariance (ANCOVA) model with treatment group and geographic region as factors and baseline value as covariate.

[c] End point in study 302 was 26 weeks for these outcomes.

Source: Clinical Study Reports for study MD-31[4] and study 302.[5]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Irritable bowel syndrome (IBS) is a common disorder of the gastrointestinal tract characterized by symptoms of abdominal pain and altered bowel habits that affect the frequency and consistency of bowel movements. Patients with IBS can either suffer from constipation (IBS-C) or diarrhea (IBS-D) or mixed IBS (IBS-M). There are no markers used to establish a definitive diagnosis of IBS, therefore it is a diagnosis of exclusion. The overall prevalence of IBS is estimated to be 10% to 15%.[1] The self-reported prevalence for IBS-C in Canada was reported to be 5.4% in 2004, and the manufacturer applied these data to the Canadian population to arrive at an estimate for prevalence of 3.9 million people in this country.[3] The strict definition of IBS is recurrent abdominal pain or discomfort at least three days per month in the past three months with two or more of: improvement with defecation, onset associated with a change in frequency of stool, or onset associated with a change in appearance of stool. IBS-D is defined as presence of loose watery stools with at least 25% of bowel movements and hard or lumpy stools with less than 25% of bowel movements, while IBS-C is defined as the reverse — hard or lumpy stools with at least 25% of bowel movements and loose or watery stools with less than 25% of bowel movements.[1,2]

1.2 Standards of Therapy

Initial management strategies for patients with mild to moderate symptoms include dietary modifications such as removal of gas-producing foods from the diet, assessment for lactose intolerance and food allergies, avoidance of gluten, and foods that contain fermentable saccharides and polyols. Among interventions, fibre, in the form of psyllium, provides overall symptom relief of IBS, although this recommendation is weak according to the American College of Gastroenterology (ACG).[2] Insoluble fibre may exacerbate symptoms such as bloating. Antispasmodics also received a weak recommendation from the ACG, as did antidepressants. With respect to antispasmodics, anticholinergic side effects may limit their use, and the quality of evidence is generally low. Recommended antidepressants included the selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants; however, adverse effects were also considered to be a limitation of these drugs, and a specific example of the constipating effects of tricyclics was given.[1,2]

1.3 Drug

Linaclotide is an orally administered guanylate cyclase-C (GC-C) agonist. Stimulation of intestinal GC-C leads to increased cyclic guanosine monophosphate (cGMP) and stimulates the cystic fibrosis transmembrane receptor (CFTR) ion channel. This leads to increased secretion of chloride and bicarbonate into the lumen and peristalsis within the gastrointestinal tract. Additionally, through stimulation of cGMP, linaclotide may also reduce intestinal pain by inhibiting nerve conduction.[3]

Linaclotide is indicated for the treatment of IBS-C in adults, and is administered at a dose of 290 mcg once daily. It is also indicated for the treatment of chronic idiopathic constipation in adults, at a dose of 145 mcg once daily.

Indication under review
For the treatment of irritable bowel syndrome with constipation (IBS-C) in adults.
Listing criteria requested by sponsor
For the treatment of IBS-C in adults.

TABLE 2: KEY CHARACTERISTICS OF TRICYCLIC ANTIDEPRESSANTS, ANTISPASMODICS, AND POLYETHYLENE GLYCOL

	Tricyclic Antidepressants	Antispasmodics	Polyethylene Glycol (PEG)
Mechanism of Action	Inhibit reuptake of serotonin and noradrenaline, also has anticholinergic effects. Intended to address the abdominal symptoms (pain); also may improve the psychological component of IBS; however, precise contribution unknown.	Hyoscine: anticholinergic	Osmotic effect on the bowel, drags water into the lumen, increasing the bulk of the stool, which in turn stimulates peristalsis
Indication[a]	Various indications unrelated to IBS-C	Relief of smooth muscle spasm of the GI or genitourinary systems	Constipation
Route of Administration	Oral	Oral	Oral
Recommended Dose	Varies depending on drug	One to two 10 mg tablets daily, maximum of six daily	Depends on formulation
Serious Side Effects/ Safety Issues	Anticholinergic side effects may become serious, including urinary retention, glaucoma, etc. Other adverse effects include sedation, sexual dysfunction, and weight gain.	Anticholinergic side effects may become serious, including urinary retention, glaucoma, etc.	None when used at recommended doses
Other	Although some tricyclic antidepressants are indicated for management of chronic pain, none have a specific indication for IBS-C	No specific indication for IBS-C, but used to relieve pain associated with spasm	

GI = gastrointestinal; IBS = irritable bowel syndrome; IBS-C = irritable bowel syndrome with constipation; PEG = polyethylene glycol.
[a] Health Canada indication.
Note: All above information gathered from product monographs in the e-CPS.[6]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of linaclotide for the treatment of irritable bowel syndrome with constipation (IBS-C) in adults.

2.2 Methods

All studies considered pivotal for regulatory approval in Canada were included in the review. Other studies were included based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients with IBS-C
Intervention	Linaclotide 290 mcg once daily
Comparators	Polyethylene glycol Fibre Antidepressants (tricyclics) Antispasmodics Placebo
Outcomes	**Key efficacy outcomes:** • Quality of life[a] • Abdominal symptoms (e.g., abdominal pain, bloating)[a] • Bowel symptoms (e.g., consistency, incomplete evacuation, straining)[a] • Frequency of complete spontaneous bowel movements • Frequency of spontaneous bowel movements **Other efficacy outcomes:** • Missed days of work/school and other measures of productivity[a] • Health care utilization (hospitalizations, emergency visits, physician visits) **Harms outcomes:** • AEs • SAEs • WDAEs • Notable harms: Gastrointestinal (diarrhea, bloating, infection)
Study Design	Published and unpublished phase 3 RCTs

AE = adverse events; IBS-C = irritable bowel syndrome with constipation; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] These outcomes were identified as important to patients in the patient 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 Constella (linaclotide).

No filters were applied to limit the retrieval by study type. 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.

The initial search was completed on February 11, 2015. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on June 17, 2015. 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 CADTH Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, databases (free), Internet search, and open access journals. 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 contact with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (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 4; excluded studies (with reasons) are presented in APPENDIX 3.

3. RESULTS

3.1 Findings From the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

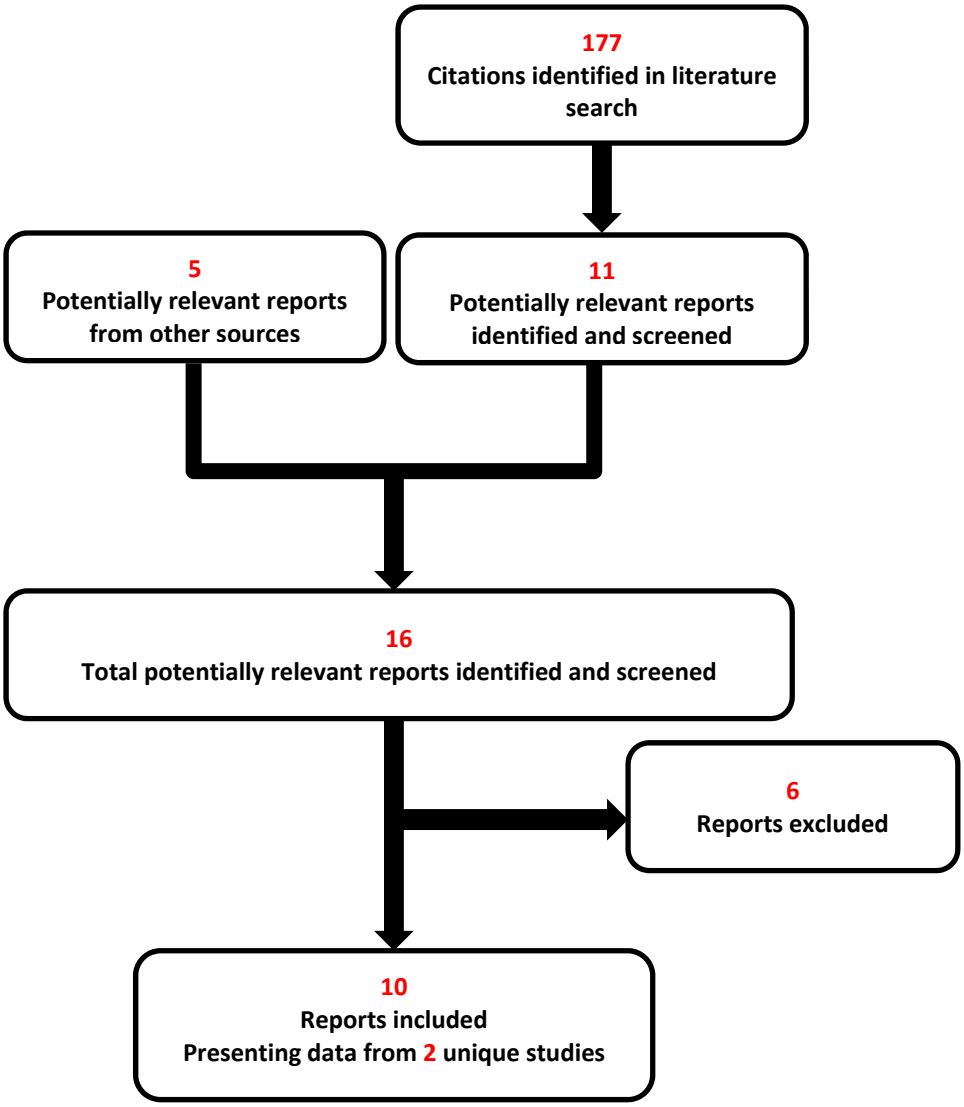


TABLE 4: DETAILS OF INCLUDED STUDIES

		MD-31	Study 302
DESIGNS & POPULATIONS	**Study Design**	DB RCT	DB RCT
	Locations	118 centres: Canada, USA	111 centres: USA
	Study period	July 14, 2009 to July 12, 2010	July 2, 2009 to September 3, 2010
	Randomized (N)	803	805
	Inclusion Criteria	Patient meets the colonoscopy requirements defined by the American Gastroenterological Association guidelines. Patient meets Rome II criteria for IBS-C: patient-reported abdominal discomfort or pain that had 2 or more of the following 3 features for at least 12 weeks, which need not be consecutive, in the 12 months before the screening visit (visit 1) or before starting chronic treatment with tegaserod or lubiprostone: a. Relieved with defecation b. Onset associated with a change in frequency of stool c. Onset associated with a change in form (appearance) of stool. Patient reports < 3 BMs (with each BM occurring in the absence of any laxative, suppository, or enema use during the preceding 24 hours) per week and reports 1 or more of the following symptoms for at least 12 weeks, which need not be consecutive, in the 12 months before the screening visit or before starting chronic treatment with tegaserod, lubiprostone, polyethylene glycol (PEG) 3350, or any laxative: a. Straining during more than 25% of BMs b. Lumpy or hard stools during more than 25% of BMs c. Sensation of incomplete evacuation during more than 25% of BMs. Average score ≥ 3.0 for abdominal pain at its worst as reported in the IVRS using an 11-point NRS during the 14 calendar days before the start of the treatment period. Patient reports an average of fewer than 3 CSBMs per week and 5 or fewer SBMs per week by the IVRS during the 14 days before the start of the treatment period.	Patient meets the colonoscopy requirements defined by the American Gastroenterological Association guidelines. Patient meets the Rome II criteria for IBS: reported abdominal discomfort or pain that had 2 or more of the following 3 features for at least 12 weeks, which need not be consecutive, in the 12 months before the screening visit, or before starting chronic treatment with tegaserod or lubiprostone: a. Relieved with defecation b. Onset associated with a change in frequency of stool c. Onset associated with a change in form (appearance) of stool. Patient reports < 3 BMs (with each BM occurring in the absence of any laxative, suppository, or enema use during the preceding 24 hours) per week and reports 1 or more of the following symptoms for at least 12 weeks, which need not be consecutive, in the 12 months before the screening visit or before starting chronic treatment with tegaserod, lubiprostone, polyethylene glycol (PEG) 3350, or any laxative: a. Straining during > 25% of BMs b. Lumpy or hard stools during > 25% of BMs c. Sensation of incomplete evacuation during > 25% of BMs. Average of < 3 CSBMs and ≤ 5 SBMs per week by the IVRS during the 14 days before the start of the treatment period.
	Exclusion Criteria	Hospitalized for a psychiatric condition or have made a suicide attempt during the 2 years before the randomization visit. Presence of any gastrointestinal	Hospitalized for a psychiatric condition or had made a suicide attempt during the 2 years before the randomization visit.

		MD-31	Study 302
		comorbidities, including impaction. Loose, "mushy" bowel movements > 25% of the time. Clinically significant findings on physical exam, laboratory tests, ECG.	Presence of any gastrointestinal comorbidities, including impaction. Loose, "mushy" bowel movements > 25% of the time. Clinically significant findings on physical exam, laboratory tests, ECG.
DRUGS	**Intervention**	Linaclotide 290 mcg PO daily	Linaclotide 290 mcg PO daily
	Comparator(s)	Placebo	Placebo
DURATION	**Phase**		
	Run-in	Screening: up to 3 weeks Pre-treatment: 2 to 3 weeks	Screening: up to 3 weeks Pre-treatment: 2 to 3 weeks
	Double-blind	12 weeks	26 weeks
	Follow-up	Randomized withdrawal phase: 4 weeks	
OUTCOMES	**Primary End Point**	Four primary end points: 1) APC 3+1 9/12 weeks responders 2) CSBM 3+1 9/12 weeks responders 3) Abdominal pain responders 9/12 weeks 4) APC +1 6/12 weeks responders	Four primary end points: 1) APC 3+1 9/12 weeks responders 2) CSBM 3+1 9/12 weeks responders 3) Abdominal pain responders 9/12 weeks 4) APC +1 6/12 weeks responders
	Other End Points	Secondary: Patient assessment of abdominal discomfort Patient assessment of bloating Stool consistency (Bristol Stool Form Scale) Patient assessment of straining Other: Patient assessment of abdominal cramping Patient assessment of abdominal fullness Per-protocol rescue medicine or any other laxative, suppository, or enema use Bowel movement within 24 Hours of receiving study drug Unsuccessful attempts to have a BM Weekly patient assessment of constipation severity Weekly patient assessment of IBS symptom severity Weekly patient assessment of degree of relief of IBS symptoms IBS-SSS assessment Treatment satisfaction assessment Treatment continuation assessment Open-ended IBS-C symptom assessments SF-MPQ-2 IBS-QOL assessment SF-12 Health Survey EQ-5D assessment WPAI:IBS-C	Secondary: Patient assessment of abdominal discomfort Patient assessment of bloating Stool consistency (Bristol Stool Form Scale) Patient assessment of straining Other: Patient assessment of abdominal cramping Patient assessment of abdominal fullness Per-protocol rescue medicine or any other laxative, suppository, or enema use Bowel movement within 24 hours of receiving study drug Unsuccessful attempts to have a BM Weekly patient assessment of constipation severity Weekly patient assessment of IBS symptom severity Weekly patient assessment of degree of relief of IBS symptoms IBS-SSS assessment Treatment satisfaction assessment Treatment continuation assessment Open-ended IBS-C symptom

		MD-31	Study 302
		HRUQ	assessments SF-MPQ-2 IBS-QOL assessment SF-12 Health Survey EQ-5D assessment WPAI:IBS-C HRUQ
NOTES	**Publications**	Rao 2012[7]	Chey 2012[8]

APC = abdominal pain and complete spontaneous bowel movement; APC +1 6/12 responder = a patient who had an abdominal pain response with an improvement of ≥ 1 complete spontaneous bowel movement (CSBM) over baseline per week in six of 12 weeks; APC 3+1 9/12 responder = a patient who had an abdominal pain response and at least three CSBMs and an improvement of ≥ 1 CSBM over baseline per week in nine of 12 weeks; BM = bowel movement; CSBM = complete spontaneous bowel movement; CSBM 3+1 9/12 responder = a patient who had at least three CSBMs and an improvement of ≥ 1 CSBM over baseline per week in nine of 12 weeks; DB = double-blind; ECG = electrocardiogram; EQ-5D = EuroQol 5-Dimensions Questionnaire; HRUQ = Health Resource Use Questionnaire; IBS = irritable bowel syndrome; IBS-C = irritable bowel syndrome with constipation; IBS-QOL = Irritable Bowel Syndrome Quality of Life measure; IBS-SSS = Irritable Bowel Syndrome–Symptom Severity Score; IVRS = interactive voice response system; NRS = numerical rating scale; PEG = polyethylene glycol; PO = orally; RCT = randomized controlled trial; SBM = spontaneous bowel movement; SF12 = Short Form (12) Health Survey; SF-MPQ-2: Short Form McGill Pain Questionnaire; WPAI:IBS-C = Work Productivity and Activity Impairment Questionnaire: Irritable Bowel Syndrome with Constipation Predominant Symptoms.
Note: Six additional reports were included (Buono 2014,[9] Williams 2014,[10] Quigley 2013,[11] manufacturer's submission,[3] FDA clinical[12] and statistical reviews[13]).
Source: Clinical Study Reports for study MD-31[4] and study 302.[5]

3.2 Included Studies

3.2.1 Description of Studies

Both study MD-31 and study 302 were multi-centre, placebo-controlled, double-blind (DB), randomized controlled trials (RCTs) sponsored by the manufacturer of linaclotide (Table 4). Both studies were North American, although only MD-31 had Canadian sites. In both studies, patients were randomized 1:1 to either linaclotide or placebo, and it was not reported whether randomization was stratified. MD-31 had a 12-week treatment period where linaclotide was compared with placebo. This was followed by a four-week randomized withdrawal phase. In this phase, patients in the linaclotide group were re-randomized to either linaclotide or placebo, and patients previously on placebo were assigned to linaclotide. Study 302 had a 26-week treatment period where linaclotide was compared with placebo.

The screening period lasted for up to 21 calendar days. During this period, patient eligibility for entry into the pre-treatment period was determined. The end of the screening period coincided with the start of the pre-treatment period. Any over-the-counter or prescription laxatives, suppositories, or enemas, and any herbal or natural drugs used to treat IBS-C were to be discontinued prior to the calendar day before the pre-treatment visit (visit 2). Likewise, non-steroidal anti-inflammatory drugs (NSAIDs), if taken for abdominal pain or discomfort, and any medicines used to treat diarrhea were to be discontinued prior to the calendar day before the pre-treatment visit. Other prohibited medicines were not to be taken during the 14 calendar days before the pre-treatment visit. The pre-treatment period was defined as the 14 calendar days (minimum) to 21 calendar days (maximum) immediately before randomization. The purpose of the pre-treatment period was to establish a baseline without therapy

and to familiarize patients with data collection methodology (i.e., interactive voice response system [IVRS]). During this period, patients had to provide the following information through daily IVRS calls:

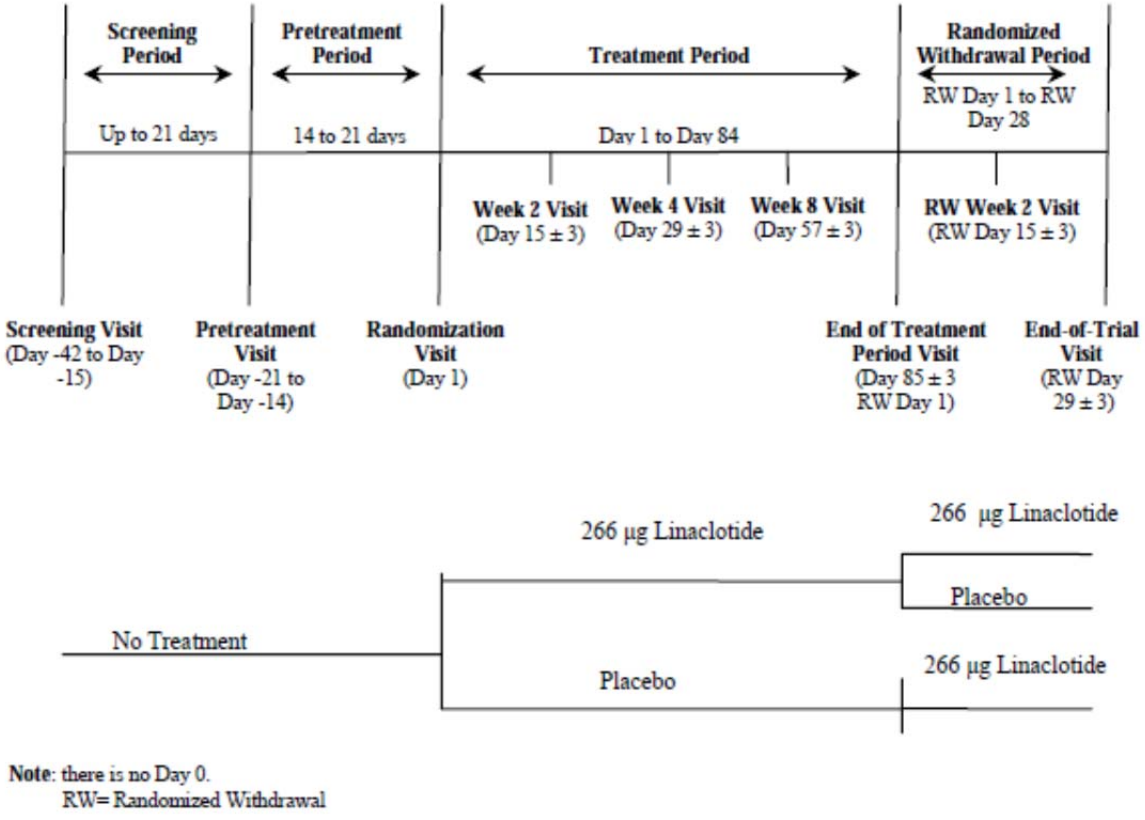
- daily bowel habits and daily patient symptom severity assessments
- weekly patient symptom severity and weekly patient global assessments
- use of per-protocol rescue medicine or any other laxatives, suppositories, or enemas.

Inclusion in the study was determined by the patients' abdominal (average score ≥ 3.0 for abdominal pain at its worst, using an 11-point numerical rating scale) and bowel symptoms (fewer than three complete spontaneous bowel movements [CSBMs] per week and five or fewer spontaneous bowel movements [SBMs] per week) in the 14-day pre-treatment period.

The randomized withdrawal (RW) period in MD-31 was defined as the four weeks immediately following the treatment period. The beginning of the RW period coincided with the end of the treatment period (ETP). Patients who completed the 12-week treatment period were eligible to enter the four-week RW period and, in a double-blind manner, were allocated to study drug as follows:

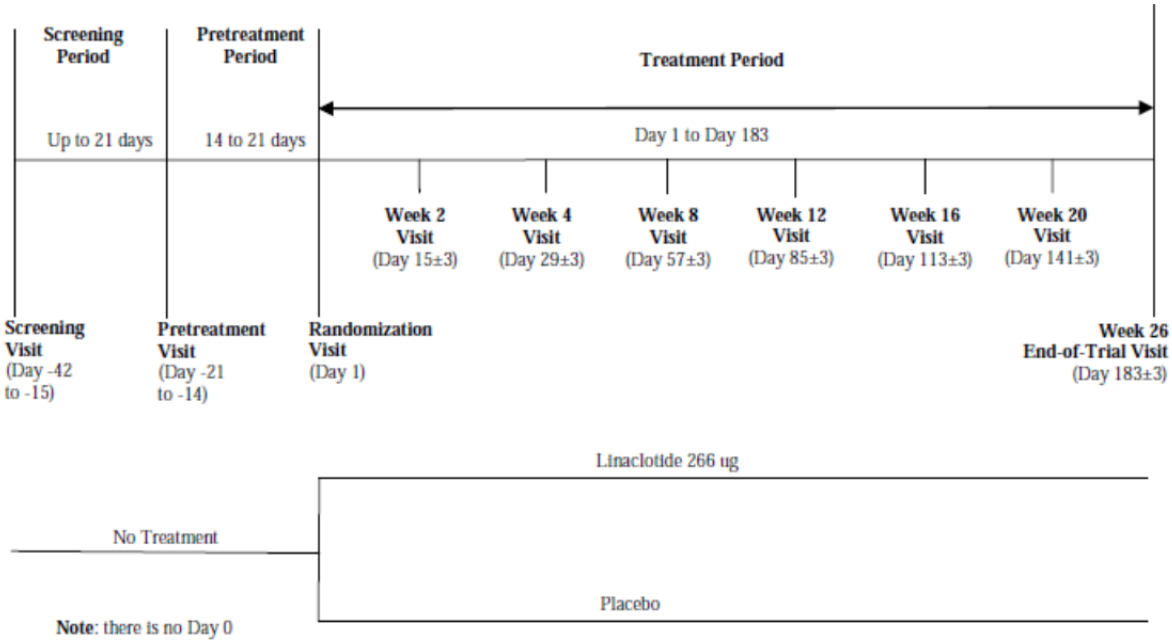
- Patients randomized to 290 mcg linaclotide during the treatment period were re-randomized to 290 mcg linaclotide or placebo (1:1).
- Patients randomized to placebo during the treatment period were assigned to 290 mcg linaclotide.

FIGURE 2: STUDY MD-31 DESIGN



Source: Clinical Study Report for study MD-31.[4]

FIGURE 3: STUDY 302 DESIGN



Source: Clinical Study Report for study 302.[5]

3.2.2 Populations

a) Inclusion and Exclusion Criteria

The included studies enrolled patients who exhibited both abdominal pain as well as classic bowel symptoms of IBS-C, including a low number (< 3) of SBMs per week, and issues with straining, consistency, and sensation of incomplete evacuation.

Patients with gastrointestinal comorbidities were excluded. Patients with mixed IBS were also excluded, as were patients with "mushy" stools more than 25% of the time. Patients also underwent an extensive screening, and were not to have any clinically significant findings on a physical exam, 12-lead electrocardiogram (ECG), or laboratory tests.

b) Baseline Characteristics

Across both studies, the majority of patients were female (~90%), with a mean age of around 44 years (Table 5). Ages were similar between groups within studies and there was a slightly higher proportion of females in the linaclotide group versus placebo in study 302 (92% versus 87% female). Various measures of disease severity were similar between groups within studies. Although mean duration of IBS-C was not reported for individual studies, in its response to the review the manufacturer reported the overall duration between the two studies as 13.2 years.[14]

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

	MD-31		Study 302	
Title	**Linaclotide (N = 405)**	**Placebo (N = 395)**	**Linaclotide (N = 401)**	**Placebo (N = 403)**
Mean (SD) age, years	43.3 (12.7)	43.7 (12.9)	44.6 (13.1)	44.0 (13.4)
Female, n (%)	367 (91)	357 (90)	368 (92)	352 (87)
Mean (SD):				
CSBM rate per week	0.2 (0.5)	0.2 (0.5)	0.2 (0.4)	0.2 (0.4)
SBM rate per week	1.9 (1.4)	1.9 (1.4)	1.7 (1.4)	1.7 (1.4)
BSFS	2.3 (1.0)	2.4 (1.0)	2.4 (1.1)	2.3 (1.0)
Abdominal pain (scale)	5.7 (1.7)	5.6 (1.7)	5.6 (1.7)	5.5 (1.7)
Abdominal discomfort (scale)	6.2 (1.6)	6.0 (1.7)	6.1 (1.7)	6.0 (1.7)
Bloating (scale)	6.7 (1.8)	6.5 (1.9)	6.6 (1.9)	6.5 (1.8)
Straining (scale)	3.6 (0.8)	3.4 (0.8)	3.6 (0.8)	3.5 (0.8)
Duration of IBS-C	NR	NR	NR	NR
Prior medication use, n (%)				
SSRI	[redacted]	[redacted]	[redacted]	[redacted]
citalopram	[redacted]	[redacted]	[redacted]	[redacted]
escitalopram	[redacted]	[redacted]	[redacted]	[redacted]
Other antidepressants				
amitriptyline	[redacted]	[redacted]	[redacted]	[redacted]
nortriptyline	[redacted]	[redacted]	[redacted]	[redacted]

BSFS = Bristol Stool Form Scale; CSBM = complete spontaneous bowel movement; IBS-C = irritable bowel syndrome with constipation; NR = not rated; SBM = spontaneous bowel movement; SD = standard deviation; SSRI = selective serotonin reuptake inhibitor.
Source: Clinical Study Reports for study MD-31[4] and study 302.[5]

3.2.3 Interventions

Patients were administered either linaclotide 290 mcg or placebo, once daily by mouth. The manufacturer initially reported the dose in the included trials as 266 mcg; however, after a reanalysis of linaclotide using a different analytical procedure, the dose expressed was changed to 290 mcg. For this reason, some of the graphs and figures in this review report the 266 mcg dose, and this number should be disregarded in favour of the 290 mcg dose.

During the pre-treatment and treatment periods, a patient could have used protocol-defined laxatives (i.e., bisacodyl tablets or bisacodyl suppositories) as rescue medicine when at least 72 hours had passed since the patient's previous bowel movement (BM) or when symptoms had become intolerable.

The use of bulk laxatives and stool softeners was allowed during the studies. Concomitant usage of bulk laxatives and docusate was generally low [redacted]. The use of docusate was similar between groups in each study, while use of bulk laxatives was similar between groups in MD-31, but numerically slightly higher with linaclotide [redacted] versus placebo [redacted] in study 302. There were other concomitant medications used during the study that have effects on the gastrointestinal tract (proton pump inhibitors [PPIs], NSAIDs), as well as drugs that may be used for IBS-C

(antidepressants); however, there were no clear differences in use between groups. Concomitant medications are further described in Table 6.

TABLE 6: CONCOMITANT MEDICATIONS USED

	MD-31		Study 302	
	Linaclotide N = 406	Placebo N = 396	Linaclotide N = 402	Placebo N = 403
[redacted]				

NSAID = non-steroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitors.
Source: Clinical Study Reports for study MD-31[4] and study 302.[5]

3.2.4 Outcomes

Each of the included studies had four primary outcomes. Abdominal pain and constipation (APC) 3+1 9/12 responders were defined as patients who were APC 3+1 responders (i.e., patients who had an abdominal pain response and at least three CSBMs and an improvement of ≥ 1 CSBM over baseline) for at least nine of the 12 weeks of the treatment period. For each week in the treatment period, a weekly APC 3+1 responder was a patient who had at least three CSBMs for the week and an increase of at least one CSBM from baseline for that week, and also had a decrease of at least 30% in the mean abdominal pain score for that week.

The next two primary efficacy parameters (CSBM 3+1 9/12 responders and abdominal pain responders 9/12 weeks) are the separate components of the first primary efficacy parameter. The fourth primary efficacy parameter was APC + 1 6/12 responders who were patients who had a decrease in abdominal pain score of at least 30%, as above, and an increase during a given week of at least one CSBM from baseline, for at least six of the 12 weeks of the treatment period. This fourth outcome is the one endorsed by the United States Food and Drug Administration (FDA).

Numerous other secondary and exploratory outcomes were assessed in the two studies, described as follows:

a) Daily Patient Assessment of Abdominal Pain at its Worst

Patient assessment of abdominal pain at its worst was collected daily by IVRS calls. The rating was provided by the patient answering the following question: "How would you rate your abdominal pain at its worst over the last 24 hours? Enter a number from 0 to 10, where 0 represents no abdominal pain and 10 represents very severe abdominal pain."

b) Spontaneous Bowel Movement and Complete Spontaneous Bowel Movement

SBM was defined as a BM that occurred in the absence of laxative, enema, or suppository use on either the calendar day of the BM or the calendar day before the BM. A CSBM was defined as an SBM that was associated with a sense of complete evacuation. The change from baseline in 12-week CSBM or SBM frequency (i.e., weekly frequency over the 12-week treatment period) was reported. The minimal clinically important difference (MCID) for mean weekly SBM is considered to be 1.9, and for mean weekly CSBM is considered to be between 1.3 and 1.5.

Each day, the patient called the IVRS and provided the number of BMs he or she had since the previous day's call. Patients were allowed to call only between the hours of 12 noon and 11:59 p.m., and they were asked to call at about the same time each day. For each BM, the patient also indicated the day the BM occurred and if the BM was associated with a sense of complete evacuation. The patient was also asked to provide assessments of consistency and straining, which were secondary efficacy assessments. The patient was also asked if he or she took any rescue medicines since the previous day's call. For each type of rescue medicine taken (e.g., bisacodyl tablet, bisacodyl suppository) or other laxatives, suppositories, or enemas, the patient was asked to indicate the day (today or yesterday) it was taken.

Patient assessment of stool consistency was collected daily by IVRS calls. For each BM, stool consistency was assessed by the patient using the Bristol Stool Form Scale (BSFS). The MCID for the BSFS is considered to be 1.6. The 7-point ordinal BSFS scale is as follows:
1 = Separate hard lumps like nuts (difficult to pass)
2 = Sausage-shaped but lumpy
3 = Like a sausage but with cracks on surface
4 = Like a sausage or snake, smooth and soft
5 = Soft blobs with clear-cut edges (passed easily)
6 = Fluffy pieces with ragged edges, a mushy stool
7 = Watery, no solid pieces (entirely liquid)

Severity of Straining

Patient assessment of straining was to be collected daily by IVRS calls. For each BM, degree of severity of straining was to be assessed by the patient using the following 5-point ordinal scale:
"How much did you strain during the bowel movement?"
1 = Not at all
2 = A little bit
3 = A moderate amount
4 = A great deal
5 = An extreme amount

The MCID for severity of straining, reported weekly, is considered to be –0.8.

Daily Patient Assessment of Abdominal Cramping

Patient assessment of abdominal cramping was collected daily by IVRS calls. The rating of abdominal cramping during the previous 24 hours on an 11-point numerical rating scale (NRS) was provided by the patient answering the following question: "How would you rate your abdominal cramping over the last 24 hours? Enter a number from 0 to 10, where 0 represents no abdominal cramping and 10 represents very severe abdominal cramping."

Daily Patient Assessment of Abdominal Fullness

Patient assessment of abdominal fullness was collected daily by IVRS calls. The rating of abdominal fullness during the previous 24 hours on an 11-point NRS was provided by the patient answering the following question: "How would you rate your abdominal fullness over the last 24 hours? Enter a number from 0 to 10, where 0 represents no abdominal fullness and 10 represents very severe abdominal fullness."

Per-Protocol Rescue Medicine or Any Other Laxative, Suppository, or Enema Use

Per-protocol rescue medicine or any other laxative, suppository, or enema use was reported by the patient daily via the IVRS. The investigator or designee reviewed rescue medicine use for each patient during each trial visit following the screening visit.

c) Exploratory

Irritable Bowel Syndrome Quality of Life Assessment

The Irritable Bowel Syndrome Quality of Life (IBS-QOL) measure is a 34-item questionnaire that assesses domains of symptoms, functional status, perceived quality of life, and social disability.[15] Respondents are asked to express their agreement with individual items according to a 5-point Likert scale: "not at all", "slightly", "moderately", "quite a bit", or "extremely or a great deal". The IBS-QOL overall score is calculated by summation, and has a potential range of 34 to 100, with a higher score indicating a better quality of life. There was no overall MCID found for IBS-QOL in IBS-C, only an MCID of 14 in a female population with predominantly IBS (Appendix 5). The IBS-QOL was self-administered at the randomization visit (visit 3) prior to the patient receiving study drug, at the end-of-treatment visit (visit 7), and at the end-of-trial (EOT) visit (visit 9). Treatment period and RW period withdrawals were to complete the self-administration of the IBS-QOL at the EOT visit (visit 9) (even if out of window).

EuroQol 5-Dimensions Questionnaire

The EuroQol 5-Dimensions Questionnaire (EQ-5D) is a generic measure of health status consisting of five questions assessing the following dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Responses to the five questions define a health state for which a utility index can be derived from published algorithms. The second component of the EQ-5D is a visual analogue scale (VAS), asking patients to rate their health from 0 to 100 (0 represents worst imaginable health state and 100 represents best imaginable health). The EQ-5D was self-administered at the randomization visit (visit 3) prior to the patient receiving study drug and all subsequent trial visits. Treatment period and RW period withdrawals were to complete the self-administration of the EQ-5D at the EOT visit (even if out of window). The MCID for index scores is estimated at 0.065. The MCID for the VAS is unknown for IBS-C.

Work Productivity and Activity Impairment Questionnaire: Irritable Bowel Syndrome with Constipation Predominant Symptoms

The Work Productivity and Activity Impairment (WPAI) questionnaire measures the impact of symptoms of a specific health condition upon work and other activities during the previous seven days.[16] The Work Productivity and Activity Impairment: Irritable Bowel Syndrome with Constipation Predominant

Symptoms (WPAI:IBS-C) questionnaire consists of six questions: employment status (employed or not employed); hours at work missed because of IBS, hours at work missed because of other reasons; hours actually worked; degree IBS affected productivity while working (VAS from 0 to 10), and degree IBS affected regular activities (VAS from 0 to 10). Patients who are employed answer all questions, while those who are not employed answer the first and last. From these, four measures are calculated. Scores are expressed as percentage of impairment/productivity loss, with higher scores indicating greater impairment. No MCID has been reported for this outcome (APPENDIX 5).[16] The WPAI:IBS-C was self-administered at the randomization visit (visit 3) prior to the patient receiving study drug and all subsequent trial visits, except the week 2 visit (visit 4) and RW period week 2 visit (visit 8). Treatment period and RW period withdrawals completed the self-administration of WPAI:IBS-C at the EOT visit (even if out of window). Higher percentages indicate greater productivity loss and activity impairment.

Health Resource Use Questionnaire

The Health Resource Use Questionnaire (HRUQ) collects information on patient demographics and health care resource use in the past four weeks prior to administration at the clinic. Information is collected on hospitalizations, outpatient visits, emergency care visits, and other health care visits. The HRUQ was to be administered by the trial coordinator at the randomization visit (visit 3) prior to the patient receiving study drug and all subsequent trial visits, except the week 2 visit (visit 4) and randomized withdrawal (RW) period week 2 visit (visit 8). Treatment period and RW period withdrawals were to have the HRUQ administered by the trial coordinator at the EOT visit (even if out of window).

3.2.5 Statistical Analysis

For each of the primary efficacy parameters, the proportion of responders in the linaclotide group was compared with the proportion in the placebo group using the Cochran–Mantel–Haenszel (CMH) test adjusting for geographic region. The study was considered positive if the test for the APC 3+1 9/12 responder parameter was statistically significant at the 0.05 level in favour of the linaclotide group.

In each of the included studies, for each of the change from baseline parameters, the linaclotide group was compared with the placebo group using an analysis of covariance (ANCOVA) model with treatment group and geographic region as fixed-effect terms and the corresponding baseline value as a covariate. Least squares mean change from baseline for each treatment group, difference in least squares mean change between the linaclotide and placebo groups, the corresponding confidence interval, and the two-sided *P* value associated with the between-group comparison were reported.

For both included studies, the overall type I family-wise error rate for testing the primary and secondary efficacy parameters was controlled at the 0.05 significance level using the following five-step serial gatekeeping multiple comparison procedure (MCP). Following this MCP, progression to the next step occurred only if all individual hypotheses within a step were rejected and the previous step(s) were all rejected at the step-specific overall significance level. If all null hypotheses within a step were not rejected, the statistical tests involved in all subsequent steps were considered not statistically significant. All hypothesis tests were two-sided.

1. The first step tested the four primary efficacy parameters using a fixed sequential testing method. The four primary efficacy parameters were each tested at the 0.05 significance level in the following fixed sequence:
   - APC 3+1 9/12 responder
   - CSBM 3+1 9/12 responder
   - Abdominal pain responder, 9/12 weeks

- APC +1 6/12 responder

If a null hypothesis was not rejected (i.e., *P* value > 0.05), all subsequent statistical tests were not considered statistically significant.

2. The second step tested the following four secondary parameters:
   - Change from baseline in 12-week CSBM frequency rate
   - Change from baseline in 12-week SBM frequency rate
   - Change from baseline in 12-week stool consistency
   - Change from baseline in 12-week severity of straining.

These four secondary parameters were tested using an overall type I error rate of 0.05 by means of a Hochberg procedure to control for multiple parameters within this step.

3. The third step tested the following three secondary parameters:
   - Change from baseline in 12-week abdominal pain
   - Change from baseline in 12-week abdominal discomfort
   - Change from baseline in 12-week bloating.

These three secondary parameters were tested using an overall type I error rate of 0.05 by means of a Hochberg (Hochberg 1988) procedure to control for multiple parameters within this step.

4. The fourth step tested the following two secondary parameters:
   - CSBM +1 6/12 responder
   - Abdominal pain responder, 6/12 weeks.

These two secondary parameters were tested using an overall type I error rate of 0.05 by means of a Hochberg (Hochberg 1988) procedure to control for multiple parameters within this step.

5. The fifth step tested the change from baseline in 12-week percentage of abdominal pain-free days at the 0.05 significance level.

For these two phase 3 trials, the sample size was planned to be approximately 800 patients, with 400 patients randomized to each of the two treatment groups: 290 mcg linaclotide and placebo. This sample size was based on consideration of the overall efficacy results of study MCP-103-202, a 12-week, phase 2b, double-blind, randomized study in 420 IBS-C patients. However, there are differences between that phase 2b study and study LIN-MD-31 that had the potential to impact responder rates — most notably the increased availability of rescue medicine and the modification to the wording, scale, and responder definition of the IVRS daily abdominal pain at its worst assessment. Given the unknown impact of these differences in study design between the phase 2b study and MD-31/study 302, it was deemed appropriate to have a larger sample size than may be indicated by solely considering the phase 2b power calculation results. For the primary outcomes, the estimates for linaclotide and placebo, respectively, were: 24.0% and 10.0% for APC 3+1 9/12 responders, 28.0% versus 12.5% for CSBM 3+1 9/12 responders, 45.3% versus 25.0% for abdominal pain 9/12 responders, and 49.3% and 27.5% for APC +1 6/12 responders.

In each study, an observed cases approach was applied to missing post-baseline data unless otherwise specified. In addition, a last observation carried forward (LOCF) approach was applied during the treatment period in sensitivity analyses for all secondary efficacy parameters that were defined on a weekly basis. In the LOCF method, a patient's last weekly value was used when the patient prematurely discontinued from the trial, or the patient's previous weekly value was used when the patient's current weekly value was missing.

Patients who were randomized but did not complete the treatment period or RW period (for study MD-31) were considered to be treatment period or RW period withdrawals, respectively, and were to complete the procedures required at the end-of-trial visit (visit 9) at the time of their discontinuation. Any patient who withdrew because of an adverse event (AE) had to be followed until the AE resolved, stabilized, or could be explained as being unrelated to study drug. The trial centres were to make a reasonable effort to follow pregnant patients until delivery or end of the pregnancy.

Subgroup analyses were specified a priori, based on gender, age, race, ethnicity, and body mass index, and were to be performed by combining results from both of the phase 3 studies, study MD-31 and study 302.

a) Analysis Populations

The safety population consisted of all patients in the randomized population who received at least one dose of double-blind study medication during the treatment period.

The intention-to-treat (ITT) population consisted of all patients in the safety population who had at least one post-randomization entry for the primary efficacy assessment (i.e., the assessment of abdominal pain at its worst or daily IVRS information that determined whether an SBM is a CSBM).

3.3 Patient Disposition

There was a relatively large number of discontinuations in MD-31 and particularly in study 302 (Table 7). In MD-31 there appeared to be more discontinuations in the linaclotide group versus placebo group. The most common reason for discontinuation with linaclotide was due to adverse events, and these were more common with linaclotide than placebo.

TABLE 7: PATIENT DISPOSITION

	MD-31		Study 302	
	Linaclotide (N = 406)	Placebo (N = 397)	Linaclotide (N = 402)	Placebo (N = 403)
Screened, N	2,424		2,340	
Screen failures	466		488	
Pre-treatment failures	1,155		1,047	
Randomized	406	397	402	403
Completed treatment period, n (%)	312 (77)	335 (84)	294 (73)	305 (76)
Discontinued, N (%)	94 (23)	62 (16)	108 (27)	98 (24)
Adverse event	32 (8)	10 (3)	41 (10)	10 (2)
Protocol violation	10 (3)	9 (2)	8 (2)	11 (3)
Withdrawal of consent	25 (6)	25 (6)	24 (6)	26 (6)
Lost to follow-up	17 (4)	10 (3)	18 (4)	13 (3)
Insufficient therapeutic response	5 (1)	4 (1)	15 (4)	33 (8)

	MD-31		Study 302	
	Linaclotide (N = 406)	Placebo (N = 397)	Linaclotide (N = 402)	Placebo (N = 403)
Other	5 (1)	4 (1)	2 (< 1)	5 (1)
ITT, N	405	395	401	403
Safety, N	406	396	402	403
Entered RW phase	312	335	NA	NA

ITT = intention-to-treat; NA = not applicable; PP = per-protocol; RW = randomized withdrawal.
Source: Clinical Study Reports for study MD-31[4] and study 302.[5]

3.4 Exposure to Study Treatments

The mean treatment duration in the 12-week study MD-31 was 75.0 days for linaclotide and 78.8 days for placebo. In study 302, which had a 26-week treatment period, mean treatment duration was 148.8 days with linaclotide and 152.6 days for placebo.

3.5 Critical Appraisal

3.5.1 Internal Validity

The proportion of patients discontinuing was relatively high in study 302, with 27% of linaclotide patients and 24% of placebo patients discontinuing by 26 weeks. In MD-31, the discontinuation rate was not as high but there was a larger proportion of linaclotide patients discontinuing compared with placebo patients (23% versus 16%). This difference can largely be accounted for by the difference in discontinuations due to an adverse event (8% versus 3%). There was also a difference in discontinuations due to adverse events in study 302 — 10% for linaclotide versus 2% for placebo. A high discontinuation rate may reduce confidence in the analysis, as the populations being compared at the end of the study might not be the same as those randomized at the beginning of the study. Imputation is typically used to try and mitigate the impact of missing data; however, in the case of differential discontinuation rates, bias may be introduced depending on the type of method used. The included studies both relied on primary outcomes that assessed response on a weekly basis, then declared a "response" based on the number of weeks that a patient responded (nine of 12 weeks for three of the primary outcomes and six of 12 weeks for the other).

The manufacturer described using an observed case method for imputation, suggesting that only complete datasets were used in the analysis. One of the limitations of using an observed case method for analysis is that results from patients who withdraw early are not accounted for in the analysis. Given that patients who are benefitting from therapy are more likely to stay in the study, using an observed case approach may overestimate the effects of an intervention. However, in the case of the included studies, an even bigger issue is that it is not clear whether a patient could still be counted as an overall responder even if he or she discontinued, as long as the patient had achieved response in nine weeks (or six weeks). Otherwise, patients discontinuing early would be less likely to be able to achieve a response, and therefore a higher rate of discontinuations with linaclotide could potentially bias results against linaclotide in the case of study MD-31, where the discontinuation rate was higher with linaclotide than placebo. If many of these patients discontinued due to treatment failure, then this differential rate might not have had as much impact on the results. However, this did not appear to be the case, as only 1% discontinued due to treatment failure in MD-31. Nevertheless, there is a lack of clarity as to how the final ITT dataset was compiled; it appears imputation was carried out in assessing the primary outcomes, given that only one or no patients are missing in each treatment group in the final ITT analysis reported. This is inconsistent with a true observed case analysis. This is a key limitation of the manufacturer's

analysis, given the high proportion of patients discontinuing in both studies, and the relatively large number of patients who were reported as "lost to follow-up". Given that the treatment effect, the difference between linaclotide and placebo, was relatively small for some of these primary outcomes, the method of imputation used could have a significant effect on results.

Many of the secondary outcomes measured symptoms on a weekly basis and then averaged them before comparing these responses to baseline, and in these cases missing values were not imputed. The risk of bias in this case depends on the trajectory of response; if patients gradually improve with linaclotide then early discontinuation may lead to bias against linaclotide, and tend to underestimate its effects. However, one would expect that patients who discontinued would be more likely to be patients whose condition was deteriorating or not improving, and in this case results may be biased in favour of linaclotide.

Health resource utilization was assessed as an exploratory outcome and it appears that patient reporting was relied upon using the HRUQ rather than directly capturing data for hospitalizations, etc. Relying on patient reporting may not be as accurate a means for assessing health resource utilization.

The use of outcomes that assess response weekly then use these weekly responses to determine overall response may not provide a complete picture of the efficacy of the study drug. For example, the APC+1 outcome, where responders only needed to respond in six of 12 weeks, does not describe the exact nature of the response to drug therapy. For example, a patient may have responded the first six weeks of therapy and lost response for the remainder of the treatment period, yet they would still be considered a responder. Linaclotide is intended to be taken chronically, and presumably the benefits of treatment would be expected to last beyond the first six weeks of therapy. Similar issues are possible with the other primary outcomes. Conversely, delayed responses would not be captured with this design, potentially underestimating the efficacy of linaclotide. The FDA performed an analysis of weekly responders for the APC 3+1 and APC +1 outcomes, and these data provide some evidence of an early peak in responses in study MD-31; however, this was not observed in study 302 (Table 11, Table 12). There was a higher proportion of discontinuations in the linaclotide group versus placebo in study MD-31, so this may have at least partially accounted for what appears to be a lower proportion of weekly responders later in the study. Although no adjustments were made for multiple comparisons, differences between linaclotide and placebo were statistically significant at each week. Therefore, although in some respects this analysis highlights the limitations in the manufacturer's responder analysis, there is no conclusive evidence that would alter the conclusions from these primary outcomes.

Both studies were double-blind, and adequate measures appear to have been taken to ensure blinding was maintained, including the use of a matching placebo. However, due to its mechanism, linaclotide would be expected to have an increased risk of gastrointestinal adverse effects — most notably diarrhea — and indeed patients who suffer from chronic constipation are likely quite familiar with diarrhea as a side effect of therapies for constipation. Therefore, the clear difference in proportion of patients experiencing diarrhea between linaclotide and placebo might have led to some degree of unblinding in the linaclotide group. Many of the outcomes in the included studies are subjective, and the risk of bias due to ascertainment of treatment assignment is greater with these outcomes.

The manufacturer defined the ITT population as all patients in the safety population who had at least one post-randomization entry for the primary efficacy assessment (i.e., the assessment of abdominal pain at its worst or daily IVRS information that determined whether an SBM is a CSBM). This is, therefore, not a true ITT analysis.

The manufacturer employed a hierarchical analysis to control for multiplicity of statistical testing. Although quality of life was assessed in the included studies, it was only as an exploratory outcome and therefore statistical analyses performed were not part of the hierarchy used to control for multiple comparisons. Thus, despite the importance of quality of life in IBS-C, the included studies were not designed to assess quality of life in a manner that could adequately control the potential for type 1 error with this outcome.

3.5.2 External Validity

The included studies did not include an active comparator for linaclotide. There are a number of drugs that are used to manage one or both of the key symptoms/signs of IBS-C, bowel symptoms (constipation), and abdominal symptoms (pain), including fibre, polyethylene glycol (PEG), antispasmodics, and tricyclic antidepressants. Therefore, the comparative efficacy and safety of linaclotide versus the existing standard of care has not been assessed. As well, rates of concurrent medications such as fibre and antidepressants were low, suggesting that therapy may not have been optimized before the addition of linaclotide.

Linaclotide employs a novel mechanism of action in managing IBS-C, and it is therefore questionable whether the included studies had sufficient follow-up to assess the long-term safety of linaclotide versus placebo. There is no cure for IBS-C and presumably no limits as to how long a patient might be expected to take linaclotide.

A significant proportion of patients were screened out in the included studies. There was a long list of inclusion/exclusion criteria, suggesting that the populations in these two studies were highly selected. For example, patients could not have any gastrointestinal comorbidities, and could not have any issues on physical exam or lab tests. There were two phases where screening occurred: the initial screening period and the pre-treatment period, where the majority of the screen failures occurred. During this pre-treatment period, patients were not allowed to take the medications they normally would for management of IBS-C, and their bowel symptoms were assessed to ensure that they did not exceed a minimum number of CSBM and SBM on a weekly basis. The large proportion of patients screened out of the included studies suggests that these were selected populations that might not be representative of the population expected to use linaclotide. Despite a large number of screened-out patients, no specific population more likely to respond to linaclotide has been articulated by the manufacturer nor identified through subgroup analyses.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported here (Section 2.2, Table 3). See APPENDIX 4 for detailed efficacy data.

3.6.1 Frequency of Complete Spontaneous Bowel Movement

The frequency of CSBM was assessed in each of the included trials and reported in a variety of ways. CSBM 3+1 response, defined as a patient who had at least three CSBMs during a given week and an increase of at least one CSBM over baseline for that week, was one of four primary outcomes, and was evaluated weekly. The efficacy end point was the proportion of patients who achieved this CSBM 3+1 response for at least nine of the 12 weeks of the study. In MD-31, the proportion of such responders was 20% in linaclotide patients and 6% of placebo patients, and this difference was statistically significant between groups (odds ratio 3.7 [95% confidence interval (CI), 2.3 to 5.9]; $P < 0.0001$) (Table 8). In study 302, the proportion of responders was 18% with linaclotide and 5% with placebo, and this

difference between groups was also statistically significant (odds ratio 4.2 [95% CI, 2.5 to 7.0]; *P* < 0.0001).

Mean CSBM frequency was reported on a weekly basis, and there was an increase from baseline in the weekly LS mean (standard error [SE]) CSBM rate in both the linaclotide (2.27 ± 0.13) and placebo (0.71 ± 0.13) groups in study MD-31. The LS mean difference between groups was 1.57 [95% CI: 1.24 to 1.90], *P* < 0.0001 (Table 8). In study 302, the increase in weekly LS mean (SE) CSBM rate was 2.24 (0.12) with linaclotide and 0.70 (0.12) with placebo, and the LS mean difference between groups was also statistically significant (1.54 [95% CI, 1.23 to 1.85]; *P* < 0.0001). The MCID for weekly CSBM is considered to be between 1.3 to 1.5, therefore these differences appear to be clinically significant. Weekly CSBM rates for both studies are also illustrated graphically (Figure 4, Figure 6).

3.6.2 Frequency of Spontaneous Bowel Movement

The frequency of SBM was reported as the change from baseline in weekly SBM. In study MD-31 there was an increase from baseline in weekly SBM rate in both the linaclotide (LS mean ± SE) (3.90 ± 0.18) and placebo (1.13 ± 0.18) groups, and this difference between groups was statistically significant (LS mean difference 2.77 (95% CI, 2.32 to 3.22); *P* < 0.0001) (Table 8). In study 302 after 12 weeks, increases in weekly SBM rate were seen in the linaclotide (LS ± SE of 4.02 ± 0.18) and placebo (1.31 ± 0.18) groups, and the difference between groups was statistically significant (LS mean difference 2.70 (95% CI, 2.26 to 3.15); *P* < 0.0001). The MCID for weekly SBM is considered to be 1.9; therefore, these differences appear to be clinically significant.

3.6.3 Abdominal Symptoms

Abdominal pain responders were patients who had achieved a 30% improvement in their abdominal pain in at least nine of the 12 weeks of the study. In MD-31, 34% of linaclotide patients and 27% of placebo patients were abdominal pain responders, and this difference between groups was statistically significant (odds ratio 1.4 [95% CI, 1.0 to 1.9]; *P* = 0.0262) (Table 8). In study 302, the proportion of abdominal pain responders was 39% with linaclotide and 20% with placebo, and this difference between groups was also statistically significant (odds ratio 2.6 [95% CI, 1.9 to 3.6]; *P* < 0.0001).

Abdominal pain was also expressed as a mean change from baseline in weekly abdominal pain scores after 12 weeks, with a LS mean (SE) change from baseline of –1.87 (0.09) with linaclotide and –1.13 ± 0.09) with placebo, for a LS MD of –0.74 (95% CI, –0.98 to –0.50), *P* < 0.0001 in study MD-31 (Table 8). In study 302 after 12 weeks, the LS mean (SE) with linaclotide was –1.85 (0.09) and with placebo was –1.07 (0.09), for a LS MD of –0.78 (95% CI, –1.02 to –0.55), *P* < 0.0001. Weekly abdominal pain scores were also reported for both studies in graphs (Figure 5, Figure 7).

Abdominal discomfort was also reported in both studies. After 12 weeks, the LS mean ± SE change from baseline in weekly scores in study MD-31 was –1.95 ± 0.10 with linaclotide and –1.21 ± 0.10 with placebo, and this difference in change was statistically significant with a LS MD of –0.74 (95% CI, –0.99 to –0.49); *P* < 0.0001 (Table 8). In study 302 after 12 weeks, the LS mean ± SE change from baseline with linaclotide was –1.94 ± 0.00 and with placebo was –1.10 ± 0.09, and this difference between groups was statistically significant, with a LS MD of –0.84 (95% CI, –1.07 to –0.60); *P* < 0.0001 (Table 8).

Bloating was also reported in both studies. After 12 weeks, the LS mean ± SE change from baseline in weekly scores in study MD-31 was –1.94 ± 0.10 with linaclotide and –1.10 ± 0.10 with placebo, and this difference in change was statistically significant with a LS mean difference of –0.84 (95% CI, –1.10 to –0.59); *P* < 0.0001 (Table 8). In study 302 after 12 weeks, the LS mean ± SE change from baseline with

linaclotide was –1.91 ± 0.09 and with placebo was –1.03 ± 0.10, and this difference between groups was statistically significant, with a LS mean difference of –0.88 (95% CI, –1.12 to –0.64); *P* < 0.0001.

3.6.4 Bowel Symptoms

Stool consistency was reported in both trials. In study MD-31, after 12 weeks the LS mean ± SE change in weekly scores compared with baseline in stool consistency was 2.07 ± 0.06 with linaclotide and 0.66 ± 0.06 with placebo, and the difference in change between groups was statistically significant, with a LS MD of 1.41 (95% CI, 1.25 to 1.57); *P* < 0.0001 (Table 8). In study 302 after 12 weeks, the LS mean ± SE with linaclotide was 1.91 ± 0.06 and with placebo was 0.61 ± 0.06, and this difference between groups was statistically significant, with a LS mean difference of 1.31 (95% CI, 1.15 to 1.47); *P* < 0.0001. The MCID for stool consistency by the BSFS is 1.6, therefore it is not clear whether these differences are clinically significant.

Straining was reported in both trials. After 12 weeks in study MD-31, the LS mean ± SE change in weekly scores compared with baseline in stool consistency was –1.31 ± 0.04 with linaclotide and –0.65 ± 0.04 with placebo, and the difference in change between groups was statistically significant, with a LS mean difference of –0.66 (95% CI, –0.76 to –0.55); *P* < 0.0001 (Table 8). In study 302 after 12 weeks, the LS mean ± SE with linaclotide was –1.24 ± 0.04 and with placebo was –0.66 ± 0.05, and this difference between groups was statistically significant, with a LS mean difference of –0.57 (95% CI, –0.69 to –0.46); *P* < 0.0001. The MCID for severity of straining is considered to be –0.8, therefore it is not clear whether these differences are clinically significant.

3.6.5 Quality of Life

Quality of life was assessed as an exploratory outcome, and therefore where analysis was reported, there was no adjustment for multiple comparisons. Therefore these data must be interpreted with caution due to the inflated risk of finding a statistically significant difference due to chance alone. [redacted]. However, with no adjustment made for multiplicity, statistical significance should not be declared for these *P* values. There was no overall MCID that could be found for IBS-QOL in this study population. An MCID of 14 was found for females with functional bowel disorder, the majority of which had IBS.

Quality of life was also assessed using the EQ-5D, once again as an exploratory outcome. No statistical analyses were provided. [redacted] (Table 8). The MCID for index scores has been estimated to be 0.065. [redacted]. No MCID was found for VAS scores in IBS.

3.6.6 Other Efficacy Outcomes

Hospitalizations were reported as part of a health resource utilization questionnaire but this was an exploratory outcome and no statistical analysis was planned (Table 10).

Absenteeism and other measures of work productivity were assessed using the WPAI:IBS-C, although this was an exploratory outcome and no statistical analyses were performed. Absenteeism was reported as the percentage of work time missed. [redacted], and a decrease from baseline in linaclotide (–1.56[redacted]) and placebo (–0.66[redacted]) groups in study 302 (Table 10). Presenteeism, the percentage day of impairment while working, was also assessed using this instrument, and there were mean ± standard deviation (SD) decreases from baseline[redacted] in both the linaclotide (–17.48[redacted]) and placebo (–11.31[redacted]) groups in study 302 (Table 10).

The use of rescue medications for laxation was reported in both studies. [redacted] (Table 10). [redacted]

TABLE 8: KEY EFFICACY OUTCOMES

	MD-31		Study 302	
	Linaclotide (N = 405)	**Placebo (N = 395)**	**Linaclotide (N = 401)**	**Placebo (N = 403)**
APC 3+1 Responder, 9/12 Weeks				
N (%)	49 (12)	20 (5)	51 (13)	12 (3)
OR (95% CI)	2.60 (1.51 to 4.47)		4.65 (2.44 to 8.84)	
P value	*P* = 0.0004[a]		*P* < 0.0001[a]	
CSBM 3+1 Responder, 9/12 Weeks				
N (%)	79 (20)	25 (6)	72 (18)	20 (5)
OR (95% CI)	3.65 (2.26 to 5.88)		4.19 (2.50 to 7.03)	
P value	*P* < 0.0001[a]		*P* < 0.0001[a]	
Abdominal Pain Responder, 9/12 Weeks				
N (%)	139 (34)	107 (27)	156 (39)	79 (20)
OR (95% CI)	1.41 (1.04 to 1.91)		2.62 (1.91 to 3.60)	
P value	*P* = 0.0262[a]		*P* < 0.0001[a]	
APC +1 Responder, 6/12 Weeks				
N (%)	136 (34)	83 (21)	135 (34)	56 (14)
OR (95% CI)	1.93 (1.40 to 2.66)		3.16 (2.22 to 4.49)	
P value	*P* < 0.0001[a]		*P* < 0.0001[a]	
12-Week CSBM Frequency Rate				
Mean (SD) baseline	0.203 (0.457)	0.238 (0.505)	0.176 (0.404)	0.213 (0.446)
Mean (SD), weeks 1 to 12	2.568 (3.088)	1.040 (1.413)	2.374 (2.949)	0.884 (1.412)
LS mean change from baseline (SE)	2.272 (0.127)	0.705 (0.128)	2.239 (0.122)	0.699 (0.122)
LS MD (95% CI)	1.568 (1.241 to 1.895)		1.540 (1.230 to 1.850)	
	P < 0.0001[b]		*P* < 0.0001[b]	
12-Week SBM Frequency Rate				
Mean (SD) baseline	1.935 (1.378)	1.897 (1.399)	1.745 (1.363)	1.739 (1.367)
Mean (SD), weeks 1 to 12	5.977 (4.382)	3.174 (2.222)	5.701 (4.225)	2.987 (2.467)

	MD-31		Study 302	
	Linaclotide (N = 405)	**Placebo (N = 395)**	**Linaclotide (N = 401)**	**Placebo (N = 403)**
LS mean change from baseline (SE)	3.898 (0.176)	1.130 (0.177)	4.017 (0.176)	1.313 (0.176)
LS MD (95% CI)	2.769 (2.315 to 3.223)		2.704 (2.255 to 3.153)	
	$P < 0.0001$[b]		$P < 0.0001$[b]	
12-Week Stool Consistency				
Mean (SD) baseline	2.260 (0.994)	2.395 (1.026)	2.381 (1.080)	2.293 (0.961)
Mean (SD), weeks 1 to 12	4.454 (1.238) N = 355	3.088 (0.955) N = 338	4.314 (1.303) N = 338	2.976 (0.921) N = 332
LS mean change from baseline (SE)	2.071 (0.060)	0.662 (0.061)	1.914 (0.063)	0.607 (0.064)
LS MD (95% CI)	1.409 (1.253 to 1.565)		1.307 (1.146 to 1.468)	
	$P < 0.0001$[b]		$P < 0.0001$[b]	
12-Week Severity of Straining				
Mean (SD) baseline	3.579 (0.756)	3.449 (0.790)	3.570 (0.817)	3.545 (0.782)
Mean (SD), weeks 1 to 12	2.164 (0.797) N = 355	2.779 (0.747) N = 338	2.295 (0.842) N = 338	2.854 (0.782) N = 332
LS mean change from baseline (SE)	–1.306 (0.042)	–0.651 (0.042)	−1.235 (0.044)	−0.663 (0.045)
LS MD (95% CI)	–0.655 (–0.763 to –0.546)		−0.572 (−0.686 to −0.459)	
	$P < 0.0001$[b]		$P < 0.0001$[b]	
12-Week Abdominal Pain				
Mean (SD) baseline	5.656 (1.648)	5.633 (1.707)	5.628 (1.738)	5.535 (1.726)
Mean (SD), weeks 1 to 12	3.653 (2.134)	4.377 (2.194)	3.683 (2.114)	4.397 (2.054)
LS mean change from baseline (SE)	–1.869 (0.093)	–1.129 (0.094)	−1.852 (0.093)	−1.070 (0.093)
LS MD (95% CI)	–0.740 (–0.981 to –0.499)		−0.782 (−1.019 to −0.545)	
	$P < 0.0001$[b]		$P < 0.0001$[b]	
12-Week Abdominal Discomfort				
Mean (SD) baseline	6.170 (1.600)	6.041 (1.672)	6.124 (1.699)	5.980 (1.690)
Mean (SD), weeks 1 to 12	4.070 (2.146)	4.721 (2.145)	4.116 (2.094)	4.851 (1.993)
LS mean change from baseline (SE)	–1.953 (0.096)	–1.211 (0.097)	–1.940 (0.002)	–1.103 (0.092)
LS MD (95% CI)	–0.742 (–0.990 to –0.494)		−0.837 (−1.071 to −0.603)	
	$P < 0.0001$[b]		$P < 0.0001$[b]	
12-Week Bloating				
Mean (SD) baseline	6.712 (1.771)	6.496 (1.890)	6.650 (1.874)	6.494 (1.819)
Mean (SD), weeks 1 to 12	4.623 (2.335)	5.306 (2.276)	4.681 (2.239)	5.445 (2.141)
LS mean change from baseline (SE)	–1.944 (0.099)	–1.100 (0.100)	−1.914 (0.094)	−1.032 (0.095)
LS MD (95% CI)	–0.844 (–1.101 to –0.587)		−0.882 (−1.123 to −0.641)	
	$P < 0.0001$[b]		$P < 0.0001$[b]	
IBS-QOL Overall Score				
Mean (SD) baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change, baseline to end point	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	
EQ-5D Index				
Mean (SD) baseline	[redacted]	[redacted]	[redacted]	[redacted]

	MD-31		Study 302	
	Linaclotide (N = 405)	**Placebo (N = 395)**	**Linaclotide (N = 401)**	**Placebo (N = 403)**
Mean (SD) change, baseline to end point	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D VAS				
Mean (SD) baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change, baseline to end point	[redacted]	[redacted]	[redacted]	[redacted]

APC = abdominal pain and complete spontaneous bowel movement; APC +1 6/12 responder = a patient who had an abdominal pain response with an improvement of ≥ 1 complete spontaneous bowel movement (CSBM) over baseline per week in six of 12 weeks; APC 3+1 responder, 9/12 weeks = a patient who had an abdominal pain response and at least three CSBMs and an improvement of ≥ 1 CSBM over baseline per week in nine of 12 weeks; CI = confidence interval; CSBM = complete spontaneous bowel movement; CSBM 3+1 responder, 9/12 weeks = a patient who had at least three CSBMs and an improvement of ≥ 1 CSBM over baseline per week in nine of 12 weeks; EQ-5D = EuroQol 5-Dimensions Questionnaire; IBS-QOL = Irritable Bowel Syndrome Quality of Life measure; LS = least squares; MD = mean difference; OR = odds ratio; SBM = spontaneous bowel movement; SD = standard deviation; SE = standard error; VAS = visual analogue scale.

[a] *P* values and odds ratio based on the Cochran–Mantel–Haenszel (CMH) test controlling for geographic region.

[b] *P* values are based on a comparison of linaclotide versus placebo in an analysis of covariance (ANCOVA) model with treatment group and geographic region as factors and baseline value as covariate.

[c] End point in study 302 was 26 weeks for these outcomes.

Source: Clinical Study Reports for study MD-31[4] and study 302.[5]

3.7 Harms

Only those harms identified in the review protocol are reported here (see 2.2.1, Protocol). See APPENDIX 4 for detailed harms data.

3.7.1 Adverse Events

Adverse events were reported after 12 weeks of therapy in MD-31, and there were 56% of linaclotide patients and 53% of placebo patients with an AE (Table 9). In study 302, after 26 weeks of therapy 65% of linaclotide patients and 57% of placebo patients reported an adverse event. The most common AE was diarrhea in both studies, occurring in 20% of linaclotide patients and 4% of placebo patients in study MD-31 and in 20% of linaclotide patients and 3% of placebo patients in study 302.

3.7.2 Serious Adverse Events

Serious adverse events (SAEs) were reported in 1% of patients after 12 weeks in each of the linaclotide and placebo groups in study MD-31, and in 1% of linaclotide and 2% of placebo patients in study 302 after 26 weeks (Table 9).

3.7.3 Withdrawals Due to Adverse Events

Withdrawals due to adverse events (WDAEs) occurred in 8% of linaclotide patients and 3% of placebo patients after 12 weeks in study MD-31, and in 10% of linaclotide patients and 2% of placebo patients after 26 weeks in study 302 (Table 9). The most common AE leading to withdrawal was diarrhea in both studies, in study MD-31 occurring in 6% of linaclotide patients and < 1% of placebo patients, and in study 302 in 5% of linaclotide patients and < 1% of placebo patients.

3.7.4 Mortality

There were no deaths in either included study.

3.7.5 Notable Harms

Notable harms were gastrointestinal, the most common of which was diarrhea, as reported above (Table 9). Other gastrointestinal adverse events included abdominal pain, occurring in 5% of linaclotide patients and 3% of placebo patients after 12 weeks in MD-31, and in 5% of linaclotide patients and 4% of placebo patients in study 302, and flatulence, occurring in 5% of linaclotide patients and 2% of placebo patients in MD-31, and 4% of linaclotide patients and 2% of placebo patients in study 302. Infectious diseases of the gastrointestinal tract were also a notable harm, and viral gastroenteritis occurred in [redacted] 4% of linaclotide patients and 2% of placebo patients in study 302.

TABLE 9: HARMS

	MD-31		Study 302	
Adverse Events	**Linaclotide (N = 406)**	**Placebo (N = 396)**	**Linaclotide (N = 402)**	**Placebo (N = 403)**
Patients with > 0 AEs, N (%)	228 (56)	210 (53)	263 (65)	228 (57)
Serious Adverse Events				
Patients with > 0 SAEs, N (%)	2 (1)	2 (1)	4 (1)	7 (2)
WDAEs				
WDAEs, N (%)	32 (8)	11 (3)	41 (10)	10 (3)
Most common reasons				
Diarrhea	23 (6)	1 (< 1)	18 (5)	1 (< 1)
Abdominal pain	[redacted]	[redacted]		
Deaths				
Number of deaths, N (%)	0	0	0	0
Notable harms				
Diarrhea	79 (20)	14 (4)	79 (20)	10 (3)
Abdominal pain	22 (5)	10 (3)	18 (5)	16 (4)
Flatulence	20 (5)	6 (2)	15 (4)	9 (2)
Viral gastroenteritis	[redacted]	[redacted]	15 (4)	9 (2)

AE = adverse event; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: Clinical Study Reports for study MD-31[4] and study 302.[5]

4. DISCUSSION

4.1 Summary of Available Evidence

Two pivotal, placebo-controlled, phase 3, DB, RCTs met the inclusion criteria for this review. Study MD-31 and study 302 each enrolled approximately 800 patients and randomized them 1:1 to either linaclotide or placebo over a treatment period of 12 and 26 weeks, respectively. The primary analyses and secondary analyses in both studies were typically carried out at week 12. Each study had four co-primary end points, and linaclotide was statistically significantly superior to placebo for each of the primary outcomes of proportion of patients achieving abdominal pain and CSBM responses in nine of 12 weeks, abdominal pain responses in nine of 12 weeks, CSBM responses in nine of 12 weeks, and APC +1 responses in six of 12 weeks. Among key secondary outcomes, linaclotide increased the number of weekly CSBM and SBM in both studies, and these differences were statistically significant. Linaclotide also improved measures of stool consistency and severity of straining versus placebo as well as abdominal symptoms like pain, discomfort, and bloating, and all of these differences were statistically significant. Quality of life was assessed using IBS-QOL overall scores, and statistically significant improvements for linaclotide versus placebo were reported in both studies; however, methodological issues including a failure to control the type 1 error rate and a lack of an MCID make the interpretation of this outcome challenging. Other outcomes such as EQ-5D, health care resource utilization, and workplace productivity were exploratory and no statistical analyses were reported. There were no deaths in either study. A limited number of SAEs were reported with no differences in incidence between groups. AEs and WDAEs were numerically more frequent with linaclotide than with placebo, although these studies were not powered to assess harms and no statistical analysis was provided. The most common AEs were gastrointestinal in nature, and diarrhea occurred in 20% of linaclotide patients and 4% of placebo patients.

4.2 Interpretation of Results

4.2.1 Efficacy

In their input to CDR for this submission, patient groups identified quality of life as a key consideration in IBS. However, the included studies were not designed specifically to assess quality of life, and instead measures of quality of life were assessed only as “other” outcomes, and statistical analyses were either not performed or were performed outside of the hierarchical testing procedure and thus must be considered to be hypothesis-generating at best. There were improvements on the IBS-QOL versus placebo in both included studies; however, once again, statistical significance cannot be declared because these analyses were performed outside of the hierarchy described a priori by the manufacturer. Therefore, despite the fact that linaclotide consistently demonstrated improvement in both bowel-related and abdominal symptoms versus placebo, the manufacturer’s study design and the lack of an MCID failed to demonstrate that these improvements translate into enhanced quality of life.

A variety of symptoms, both abdominal (e.g., pain) and bowel-related, were improved with linaclotide versus placebo in both studies, and linaclotide was superior to placebo for all four co-primary outcomes. The magnitude of the treatment effect versus placebo appears modest for some of these dichotomous outcomes. Of the four primary outcomes, the largest treatment effect across both studies (13% in MD-31 and 20% in study 302) was reported for APC +1 6/12 responders, and this was the outcome endorsed by the FDA. This was the only one of the four primary outcomes that required a response in only one-half of the total 12 weeks; the others all required a given response in nine of 12 weeks. The outcome with the lowest response was APC 3+1 9/12 reponders, with a treatment effect of only 7% in MD-31 and

10% in study 302. This outcome is considered to have low sensitivity (APPENDIX 5). Nonetheless, these are the only two outcomes that combine both abdominal pain and bowel symptoms (APC); however, the FDA-endorsed outcome is not as conservative as that used by the manufacturer. Both of these outcomes are important in IBS-C, and ideally patients would experience significant improvement in each. There were more abdominal pain responders than CSBM responders, although it is not clear whether this was due to how response was defined for these outcomes or whether linaclotide has a proportionately greater impact on pain than on bowel symptoms.

In an attempt to address the small proportion of responders in many of the primary analyses, Lacy et al. published a pooled post hoc analysis of the FDA primary outcome, APC +1.[17] The objective of the post hoc analysis was to evaluate clinical response in patients who did not meet this FDA primary outcome of an APC +1 response for 6/12 weeks of the study. This post hoc analysis was supported by the manufacturer of linaclotide. The proportion of responders with linaclotide was 34% at 12 weeks in each of the two included studies and 17% across the placebo groups of these two studies. The Lacy et al. paper focused on patients who were non-responders by this FDA definition of response, through a variety of less conservative measures of response — either global or one of the key components of the definition (bowel or abdominal symptoms). The global measures, described as Patient Rating of Change Questions (PRCQs) were assessed as exploratory outcomes in the included studies, and positive responses (abdominal pain or stool frequency being improved or somewhat improved) were reported. However, when looking at the proportions of patients who had reported at least "somewhat" for relief of abdominal symptoms, although the proportion appeared relatively high with linaclotide across studies, 63% (95% CI, 59% to 68%), the placebo response was 48% (95% CI, 44% to 51%). Therefore, the treatment effect was not any larger than with the original FDA outcome. A relatively small treatment effect and often a large placebo response was a consistent finding with a number of reported outcomes.[17] Although additional "responders" were identified with these less conservative definitions, in many cases this occurred in both the linaclotide and placebo groups.

As noted, the primary outcomes all assessed a given response on a weekly basis, and an overall responder was determined by the number of weeks a patient responded, a minimum of nine of 12 weeks for three of the primary outcomes, and six of 12 weeks for the other. What is not known is the timing of these responses, i.e., whether they all occurred early or late in the treatment period. For the outcome that required response in only six of 12 weeks, for example, patients could have responded early in the treatment period, and then lost their response as the treatment period progressed. Conversely, late responders would also not be captured under this design. The FDA performed an analysis of two of the primary outcomes (APC 3+1 and APC +1 responders), and there were different findings between the two studies (Table 11, Table 12). Although a statistically significant difference (albeit unadjusted for multiple comparisons) between linaclotide and placebo is maintained from week to week, there is some indication in study MD-31 that the proportion of responders peaked early (weeks 3 to 4) and diminished near the end of the study. This early peak was not observed in study 302, and because a statistically significant difference between groups was maintained at all weeks, one cannot conclude that this type of responder outcome biased results across the two studies. The manufacturer also presented graphs reporting the mean responses per week for the key efficacy outcomes such as CSBM frequency and change from baseline in abdominal pain scores. There is clearly a downward trend (improvement) in abdominal pain scores for linaclotide from week to week throughout the 12-week treatment period. The same trend is seen in the placebo group, although the magnitude of improvement is smaller. For weekly CSBM frequency, the trend is flatter, but still suggests that response was maintained over the course of the 12-week treatment period where the primary outcomes were assessed.

The included studies were placebo-controlled and therefore no conclusions can be drawn regarding the efficacy or harms of linaclotide compared with other drugs that might be used to manage IBS-C in Canada. The management of IBS-C is complicated by the fact that the two key overall goals of therapy — treatment of constipation and abdominal pain — can be and often are managed separately. IBS-C also has a psychological component that is not well understood, and this also plays a role in management. For example, antidepressants are used to manage IBS-C, however the only class currently recommended under US guidelines are tricyclic antidepressants, which are also used in management of chronic pain.[2] Tricyclics are known for their anticholinergic side effects, including constipation, which would certainly be a disadvantage in IBS-C. Many of the drugs used to specifically address constipation, such as fibre, are inexpensive and available in a wide variety of forms (including from the diet) without a prescription. A potential advantage of linaclotide is that it addresses both of these key symptoms of IBS-C; however, it is not clear whether it represents an efficacy advantage in addressing each symptom, individually. For example, given the availability of fibre, it is not clear whether linaclotide improves constipation in addition to existing therapies used by patients, given that concurrent use of therapies such as fibre were low in the trial. A direct comparison of these two drugs, or others, would have helped to answer some of these questions regarding relative benefit. No indirect comparisons of these drugs with linaclotide were provided by the manufacturer or identified in the literature.

The use of health care resources is an important component of the economics of linaclotide. The included studies were, however, not designed to assess health care resource utilization. Although it was assessed as an exploratory outcome, the number of events was too small to notice any trends, and no statistical analysis was planned. Therefore at present, the impact of linaclotide on health care resource utilization is unknown.

4.2.2 Harms

Although the included studies are likely too short in duration to assess long-term harms, given the novel mechanism employed by linaclotide, the harms data available thus far suggest that its major adverse effects are gastrointestinal in nature, mainly diarrhea. Diarrhea is an adverse effect that is frequently seen with drugs used to treat constipation. The disease course of IBS-C can fluctuate, and it is possible that diarrhea is indicative of changes in the nature of bowel symptoms. It is not clear whether certain patients will need to take linaclotide on an ongoing basis or will be able to adjust administration of linaclotide with the course of IBS-C. In the open-label extensions, with mean treatment duration of around one year, diarrhea remained the most common AE, and no new or unexpected safety signals were reported. There was a large proportion of patients who were screened out of the included studies, due to what appear to be quite stringent enrolment criteria. Many of the patients who did not meet enrolment criteria for the included studies were allowed into the extension, and it is noteworthy that these patients appeared to have a higher incidence of diarrhea than the original randomized population. This might suggest that use of linaclotide in a wider population may be associated with a higher risk of diarrhea than expected given the results of the DB RCT phases of the included studies.

5. CONCLUSIONS

Two multicentre, manufacturer-sponsored, placebo-controlled, DB RCTs — study MD-31 and study 302 — met the inclusion criteria for this review. The studies each enrolled approximately 800 patients with IBS-C, exhibiting both symptoms of constipation and abdominal pain, and randomized them 1:1 to either linaclotide or placebo. Study MD-31 compared linaclotide with placebo over a 12-week treatment period, while study 302 compared linaclotide with placebo over a 26-week treatment period. Both studies had four primary outcomes assessed at 12 weeks: proportion of responders with respect to abdominal pain, CSBMs, and two composites that combined abdominal pain and improvement in CSBMs. Linaclotide was associated with statistically superior improvements in each of the four primary outcomes in both studies. Several other measures of abdominal and bowel symptoms were also reported as secondary outcomes, and these were all statistically significantly improved versus placebo. Quality of life was assessed only as an exploratory outcome, therefore although statistically, but not clinically, significant improvements for linaclotide over placebo were reported on a disease-specific instrument, these findings must be considered hypothesis-generating. Given that overall response rates to the primary outcomes were low in a highly selective population, balanced with high withdrawal rates and high observed rates of adverse effects and low usage of concurrent therapies, the clinical benefit of linaclotide in the general population is uncertain.

APPENDIX 1: PATIENT INPUT SUMMARY

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

1. Brief Description of Patient Group Supplying Input

The GI (Gastrointestinal) Society is committed to improving the lives of people with GI and liver conditions by supporting research, advocating for patient access in health care, and promoting GI and liver health. It provides evidence-based information through the BadGut Basics patient information pamphlet and the Inside Tract/Du Coeur au ventre newsletter, BadGut lectures, GI support group meetings, continuing education events for health care professionals; it also has two websites, one in English (www.badgut.org) and one in French (www.mauxdeventre.org). In the last two years, the GI Society has received funding from Abbott Laboratories Ltd, AbbVie Corporation, Amgen Canada Inc, Actavis (as Aptalis Pharma, Forest Laboratories, and Warner Chilcott), AstraZeneca Canada Inc., Bristol-Myers Squibb Canada, Canada's Research-Based Pharmaceutical Companies (Rx&D), Ferring Inc., Gilead Sciences Canada Inc., GlaxoSmithKline Inc., Hoffmann-La Roche Ltd., Janssen Canada, Merck Canada Inc., Medical Futures Inc., Cubist Pharmaceuticals (as Optimer Pharma), Pfizer Canada Inc., Sanofi-Aventis Canada Inc., Takeda Canada Inc., and Vertex Pharmaceuticals (Canada) Inc.

The GI Society declared no conflicts of interest in preparing its submission.

2. Condition and Current Therapy-Related Information

Information was obtained through the use of an online survey, interviews with patients who were part of the Constella clinical trial, and information written by physicians for the GI Society's publications.

Patients with irritable bowel syndrome (IBS) whose predominant symptom is constipation have what is termed irritable bowel syndrome with constipation (IBS-C). These patients account for approximately one-third of IBS patients. Patients experience a slowly contracting digestive system, which subsequently delays the transit time for the products of digestion thus leading to constipation. Patients experience symptoms such as increased pressure on the bowels, bloating, abdominal cramping, back pain, general malaise, poor appetite, feelings of rectal pressure or fullness, and a sensation of incomplete evacuation. In addition, hemorrhoids, anal fissures, diverticular disease, rectal bleeding, and rectal prolapse are often experienced as complications from intense straining while trying to pass stool.

Everyday activities can be negatively affected, such as the ability to care for family members, go grocery shopping, sit at a desk, and move regularly (including walking and exercise). Aside from occassional unrelenting pain and bloating, patients often experience pain during sex due to pelvic floor dysfunction, in addition to debilitating fatigue. All of these symptoms lead to increased isolation, depression, a sense of demoralization, and social stigma. Incapacitation due to the symptoms of IBS-C can decrease the ability of the working parent to care for his or her family and can cause the patient to miss work, and this absence from work has caused some patients to lose their jobs. Children with IBS-C may miss out on social opportunities and school, thus potentially affecting their social development, while seniors with IBS-C can suffer from additional isolation from having to miss social interactions. In addition, they also lose even more of their independence.

Caregivers are mostly affected when currently available treatments for IBS-C do not work, leaving the patient unable to perform his or her regular activities or complete day-to-day activities such as errands, cooking, and hygiene. The caregiver must then perform these tasks in addition to taking care of patient.

Caregivers are also responsible for taking patients to hospitals should the need arise, which can lead to loss of personal time. The health system is also adversely affected when treatments are ineffective, as the patients use hospital and health services more frequently.

Currently available therapy includes diet and exercise, physiotherapy, bulk-forming laxatives, stool softeners, enemas, lubricants, stimulants, and hyperosmotics. While diet and exercise often help those with occasional or mild constipation, they are not sufficient for chronic IBS-C. Physiotherapy for pelvic dysfunction helps some patients but is usually only beneficial with the addition of other treatments such as laxatives (which are not suitable for long-term use). Bulk-forming laxatives (such as Metamucil, Benefibre, and Prodiem) are safe for long-term use but can adversely affect the patient (by inducing some of the aforementioned symptoms) and they are not quick-acting. Stool softeners (such as Colace) are also safe for long-term use, but are not effective for patients suffering from IBS-C. Conversely, enemas and lubricants (such as mineral oil) are quick-acting, but neither is suitable for long-term use. Stimulants (such as Ex-lax, Dulcoax, castor oil, senna tea, and Senokot) should be used only very short-term and under the supervision or either a physician or pharmacist; these are also not effective for the IBS-C patient. Finally, hyperosmotics (saline, magnesium preparations, sulfate salts and sodium phosphates, and glycerine) can additionally cause electrolyte imbalances and increase thirst and dehydration. Patients often reported that the side effects of using these therapies were terrible, that they were expensive in the long run due to the constant use, and that they worsened the patients' condition.

3. Related Information About Constella

Constella is expected to enable patients with IBS-C to function normally in life with regard to their jobs, family responsibilities, and social activities. The need for an additional choice regarding effective treatment is anticipated enthusiastically, as is an easier and more reliable option. There is hope that this will enable the patient to cease juggling numerous ineffective treatment regimens in order to regulate their bowel function and begin leading normal lives.

Patients who had access to Constella (either through a clinical trial or private drug plan use) reported an "astounding" change when using the drug. The bloating and cramping ceased in some patients, while others reported that their stool habits had changed significantly; stools went from rock hard to normal or bowel movements increased from once a week to every day. Patients also reported that their lives had immensely improved and that Constella improved their whole system.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	February 11, 2015
Alerts:	Weekly search updates until June 17, 2015.
Study Types:	No search filters were applied
Limits:	No language or date limits Human only 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	Requires words are adjacent to each other (in any order)
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
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	(Constella or linaclotide* or linzess* or MD1100 or MD-1100).ti,ab,rn,nm,sh,hw,ot.
2	(851199 59 2 or "851199592" or 851199 592 or 85119959 2 or 851199 60 5 or "851199605" or 85119960 5 or 851199 605).rn,nm.
3	1 or 2
4	3 use pmez
5	*linaclotide/
6	(linaclotide* or Constella or linzess* or MD1100 or MD-1100).ti,ab.
7	5 or 6
8	7 use oemezd
9	4 or 8
10	exp animals/
11	exp animal experimentation/ or exp animal experiment/
12	exp models animal/
13	nonhuman/
14	exp vertebrate/ or exp vertebrates/
15	animal.po.
16	or/10-15
17	exp humans/
18	exp human experimentation/ or exp human experiment/
19	human.po.
20	or/17-19
21	16 not 20
22	9 not 21
23	22 not conference abstract.pt.
24	remove duplicates from 23

OTHER DATABASES	
PubMed	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:	February 9, 2015
Keywords:	Drug name, Indication
Limits:	No language or date limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/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
Atluri DK, Chandar AK, Bharucha AE, Falck-Ytter Y. Effect of linaclotide in irritable bowel syndrome with constipation (IBS-C): a systematic review and meta-analysis. Neurogastroenterol Motil. 2014 Apr;26(4):499-509.	Review
Johnston JM, Kurtz CB, MacDougall JE, Lavins BJ, Currie MG, Fitch DA, et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. Gastroenterology. 2010 Dec;139(6):1877-86.	Not phase 3
Chang L, Lembo AJ, Lavins BJ, Shiff SJ, Hao X, Chickering JG, et al. The impact of abdominal pain on global measures in patients with chronic idiopathic constipation, before and after treatment with linaclotide: a pooled analysis of two randomised, double-blind, placebo-controlled, phase 3 trials. Aliment Pharmacol Ther [Internet]. 2014 Dec [cited 2015 Feb 27];40(11-12):1302-12. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4278547/pdf/apt0040-1302.pdf	Indication not of interest
Camilleri M, Lembo AJ, Lavins BJ, MacDougall JE, Carson RT, Williams VS, et al. Comparison of adequate relief with symptom, global, and responder endpoints in linaclotide phase 3 trials in IBS-C. United European Gastroenterol J [Internet]. 2015 Feb [cited 2015 Feb 27];3(1):53-62. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4315678/pdf/10.1177_2050640614555946.pdf	Subgroup analysis
Lacy BE, Lembo AJ, MacDougall JE, Shiff SJ, Kurtz CB, Currie MG, et al. Responders vs clinical response: a critical analysis of data from linaclotide phase 3 clinical trials in IBS-C. Neurogastroenterol Motil [Internet]. 2014 Mar [cited 2015 Feb 27];26(3):326-33. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4282394/pdf/nmo0026-0326.pdf	Subgroup analysis
Rao SS, Quigley EM, Shiff SJ, Lavins BJ, Kurtz CB, MacDougall JE, et al. Effect of linaclotide on severe abdominal symptoms in patients with irritable bowel syndrome with constipation. Clin Gastroenterol Hepatol. 2014 Apr;12(4):616-23.	Subgroup analysis

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 10: OTHER EFFICACY OUTCOMES

	MD-31		Study 302	
	Linaclotide (N = 405)	**Placebo (N = 395)**	**Linaclotide (N = 401)**	**Placebo (N = 403)**
WPAI:IBS-C Absenteeism				
Mean (SD) baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change, baseline to end point	[redacted]	[redacted]	-1.56 [redacted]	-0.66 [redacted]
WPAI:IBS-C Presenteeism				
Mean (SD) baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change, baseline to end point	[redacted]	[redacted]	-17.48 [redacted]	-11.31 [redacted]
WPAI:IBS-C Productivity Loss				
Mean (SD) baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change, baseline to end point	[redacted]	[redacted]	-19.18 [redacted]	-11.18 [redacted]
WPAI:IBS-C Daily Activity Impairment				
Mean (SD) baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change, baseline to end point	[redacted]	[redacted]	-19.28 [redacted]	-12.87 [redacted]
Hospitalizations (Days)				
Mean (SD) baseline, days	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change, baseline to end point	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalizations (number)				
Mean (SD) baseline, n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change, baseline to end point	[redacted]	[redacted]	[redacted]	[redacted]
ED Visits				
Mean (SD) baseline, n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change, baseline to end point	[redacted]	[redacted]	[redacted]	[redacted]
Office Visits				
Mean (SD) baseline, n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change, baseline to end point	[redacted]	[redacted]	[redacted]	[redacted]

	MD-31		Study 302	
	Linaclotide (N = 405)	**Placebo (N = 395)**	**Linaclotide (N = 401)**	**Placebo (N = 403)**
Rescue Medication Use				
Mean days (SD) baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean days (SD) change from baseline during treatment period	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]		[redacted]	
	[redacted]		[redacted]	

CI = confidence interval; ED = emergency department; LS = least squares; MD=mean difference; SD = standard deviation; SE = standard error; WPAI:IBS-C = Work Productivity and Activity Impairment Questionnaire: Irritable Bowel Syndrome With Constipation Predominant Symptoms.
[a] *P* values and odds ratio based on the Cochran–Mantel–Haenszel (CMH) test controlling for geographic region.
[b] *P* values are based on a comparison of linaclotide versus placebo in an analysis of covariance (ANCOVA) model with treatment group and geographic region as factors and baseline value as covariate.
[c] End point for these outcomes in study 302 was 26 weeks.
Source: Clinical Study Reports for study MD-31[4] and study 302.[5]

TABLE 11: WEEKLY APC 3+1 RESPONDERS BY TREATMENT GROUP, INTENTION-TO-TREAT POPULATION

Study MD-31	Linaclotide	Placebo	Difference	*P* Value (Chi Square)
Week 1	70 (17)	24 (6)	11%	*P* < 0.0001
Week 2	82 (20)	40 (10)	10%	*P* < 0.0001
Week 3	102(25)	32 (8)	17%	*P* < 0.0001
Week 4	114 (28)	49 (12)	16%	*P* < 0.0001
Week 5	101 (25)	46 (12)	13%	*P* < 0.0001
Week 6	110 (27)	53 (13)	14%	*P* < 0.0001
Week 7	96 (24)	53 (13)	10%	*P* < 0.0001
Week 8	98 (24)	53 (13)	11%	*P* < 0.0001
Week 9	92 (23)	55 (14)	9%	*P* = 0.0013
Week 10	86 (21)	46 (12)	10%	*P* = 0.0002
Week 11	88 (22)	55 (14)	8%	*P* = 0.0038
Week 12	90 (22)	43 (11)	11%	*P* < 0.0001
Study 302	**Linaclotide**	**Placebo**	**Difference**	***P* Value (Chi Square)**
Week 1	51 (13)	16 (4)	9%	*P* < 0.0001
Week 2	81 (20)	20 (5)	15%	*P* < 0.0001
Week 3	88 (22)	33 (8)	14%	*P* < 0.0001
Week 4	95 (24)	31 (8)	16%	*P* < 0.0001
Week 5	92 (23)	37 (9)	14%	*P* < 0.0001
Week 6	97 (24)	33 (8)	16%	*P* < 0.0001
Week 7	95 (24)	36 (9)	15%	*P* < 0.0001
Week 8	103 (26)	27 (7)	19%	*P* < 0.0001
Week 9	85 (21)	33 (8)	13%	*P* < 0.0001
Week 10	89 (22)	40 (10)	12%	*P* < 0.0001
Week 11	86 (21)	33 (8)	13%	*P* < 0.0001
Week 12	103 (26)	40 (10)	16%	*P* < 0.0001

Week 13	96 (24)	38 (9)	15%	*P* < 0.0001
Week 14	97 (24)	35 (9)	16%	*P* < 0.0001
Week 15	86 (21)	36 (9)	13%	*P* < 0.0001
Week 16	92 (23)	35 (9)	14%	*P* < 0.0001
Week 17	92 (23)	41 (10)	13%	*P* < 0.0001
Study 302	**Linaclotide**	**Placebo**	**Difference**	***P* Value (Chi Square)**
Week 18	87 (22)	38 (9)	12%	*P* < 0.0001
Week 19	92 (23)	43 (11)	12%	*P* < 0.0001
Week 20	83 (21)	36 (9)	12%	*P* < 0.0001
Week 21	88 (22)	33 (8)	14%	*P* < 0.0001
Week 22	95 (24)	32 (8)	16%	*P* < 0.0001
Week 23	86 (21)	36 (9)	13%	*P* < 0.0001
Week 24	82 (20)	40 (10)	11%	*P* < 0.0001
Week 25	91 (23)	37 (9)	14%	*P* < 0.0001
Week 26	79 (20)	27 (7)	13%	*P* < 0.0001

APC 3+1 responder = a patient who had an abdominal pain response and at least three complete spontaneous bowel movements and an improvement of ≥ 1 complete spontaneous bowel movement over baseline per week.
Source: FDA Statistical Review.[13]

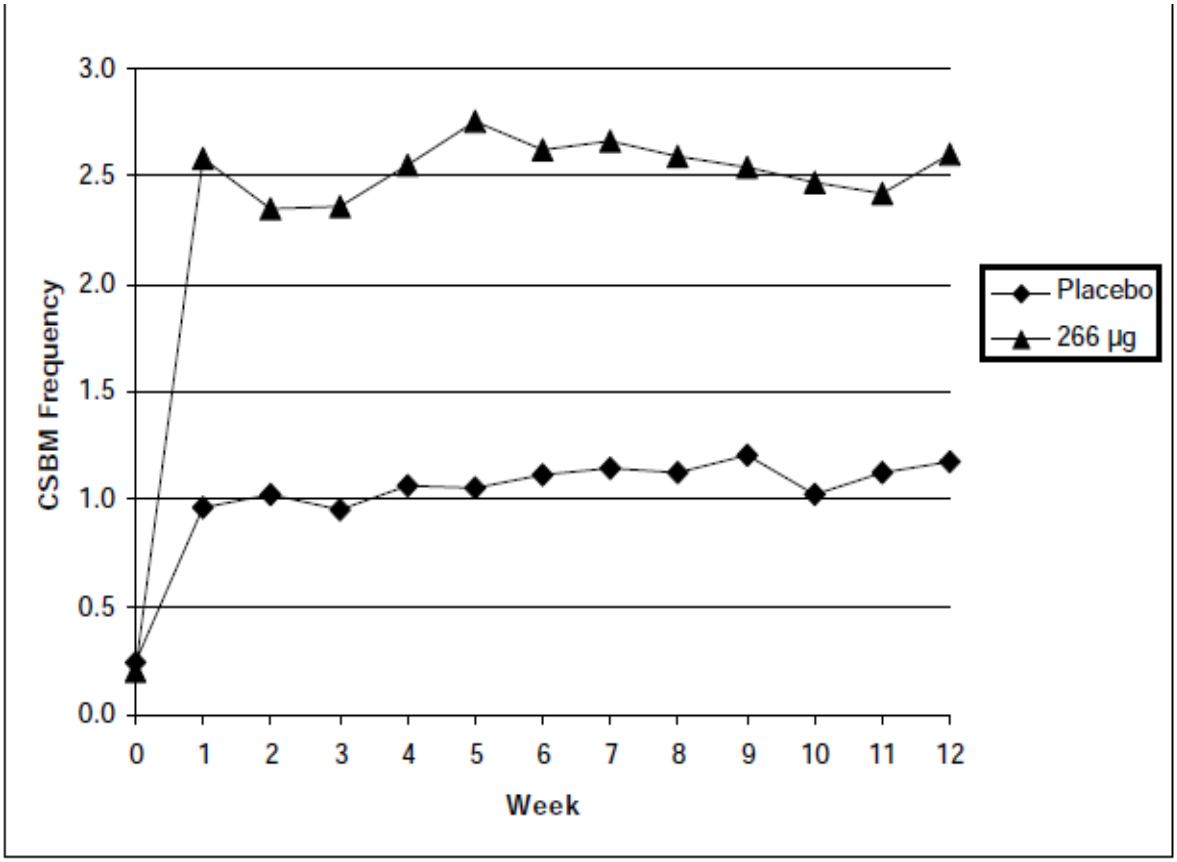
TABLE 12: WEEKLY APC +1 RESPONDERS BY TREATMENT GROUP, INTENTION-TO-TREAT POPULATION

Study MD-31	**Linaclotide**	**Placebo**	**Difference**	***P* Value (Chi Square)**
Week 1	87 (22)	39 (10)	12%	*P* < 0.0001
Week 2	108 (27)	69 (18)	9%	*P* = 0.00016
Week 3	134 (33)	68 (17)	16%	*P* < 0.0001
Week 4	143 (35)	76 (19)	16%	*P* < 0.0001
Week 5	140 (35)	74 (19)	16%	*P* < 0.0001
Week 6	147 (36)	83 (21)	15%	*P* < 0.0001
Week 7	130 (32)	86 (22)	10%	*P* = 0.0009
Week 8	126 (31)	87 (22)	9%	*P* = 0.0033
Week 9	130 (32)	91 (23)	9%	*P* = 0.0038
Week 10	125 (31)	75 (19)	12%	*P* = 0.0002
Week 11	129 (32)	91 (23)	9%	*P* = 0.0050
Week 12	120 (30)	81 (21)	9%	*P* < 0.0026
Study 302	**Linaclotide**	**Placebo**	**Difference**	***P* Value (Chi Square)**
Week 1	78 (20)	29 (7)	12%	*P* < 0.0001
Week 2	115 (29)	46 (11)	17%	*P* < 0.0001
Week 3	130 (32)	63 (16)	17%	*P* < 0.0001
Week 4	131 (33)	56 (14)	19%	*P* < 0.0001
Week 5	141 (35)	73 (18)	17%	*P* < 0.0001
Week 6	148 (37)	70 (17)	20%	*P* < 0.0001
Week 7	134 (33)	67 (17)	17%	*P* < 0.0001
Week 8	133 (33)	64 (16)	17%	*P* < 0.0001
Week 9	137 (34)	59 (15)	20%	*P* < 0.0001
Week 10	132 (33)	70 (17)	16%	*P* < 0.0001
Week 11	133 (33)	68 (17)	16%	*P* < 0.0001

Week 12	137 (34)	61 (15)	19%	*P* < 0.0001
Week 13	132 (33)	60 (15)	18%	*P* < 0.0001
Week 14	125 (31)	56 (14)	17%	*P* < 0.0001
Week 15	123 (31)	62 (15)	15%	*P* < 0.0001
Week 16	135 (34)	66 (16)	17%	*P* < 0.0001
Study 302	**Linaclotide**	**Placebo**	**Difference**	***P* Value (Chi Square)**
Week 17	129 (32)	57 (14)	18%	*P* < 0.0001
Week 18	121 (30)	67 (17)	14%	*P* < 0.0001
Week 19	122 (30)	64 (16)	15%	*P* < 0.0001
Week 20	123 (31)	68 (17)	14%	*P* < 0.0001
Week 21	130 (32)	60 (15)	18%	*P* < 0.0001
Week 22	125 (31)	54 (13)	18%	*P* < 0.0001
Week 23	119 (30)	60 (15)	15%	*P* < 0.0001
Week 24	114 (28)	59 (15)	14%	*P* < 0.0001
Week 25	123 (31)	60 (15)	16%	*P* < 0.0001
Week 26	104 (26)	48 (12)	14%	*P* < 0.0001

APC +1 responder = a patient who had an abdominal pain response with an improvement of ≥ 1 complete spontaneous bowel movement over baseline per week.
Source: FDA Statistical Review.[13]

FIGURE 4: WEEKLY MEAN COMPLETE SPONTANEOUS BOWEL MOVEMENT RATE IN STUDY MD-31

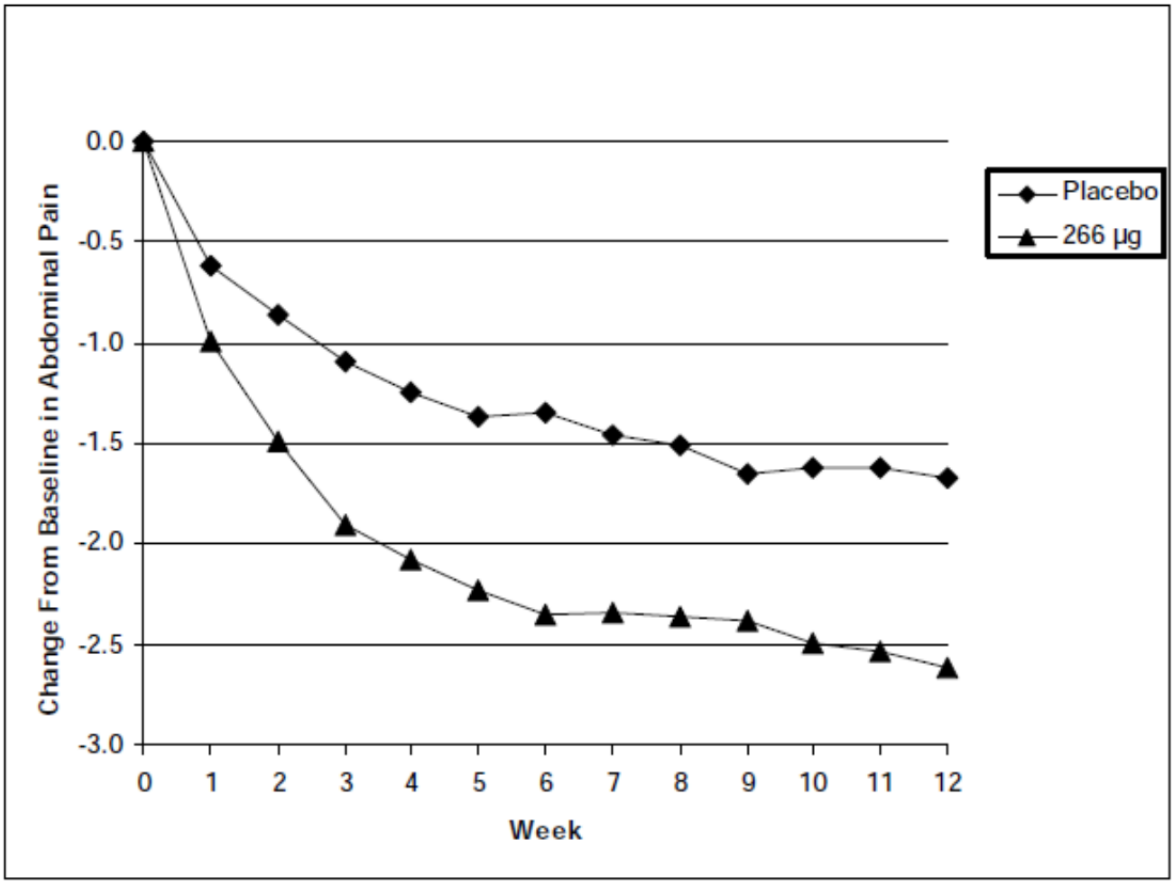


Weekly p-values < 0.0001 for all linaclotide measurements versus placebo; comparisons were based on an ANCOVA change from baseline model with treatment group and geographic region factors and baseline value as covariate. ANCOVA = analysis of covariance; CSBM = complete spontaneous bowel movement; ITT = intent-to-treat; OC = observed cases.

Source: Table 14.4.2.1B.

Source: Clinical Study Report for study MD-31.[4]

FIGURE 5: WEEKLY MEAN ABDOMINAL PAIN IN STUDY MD-31



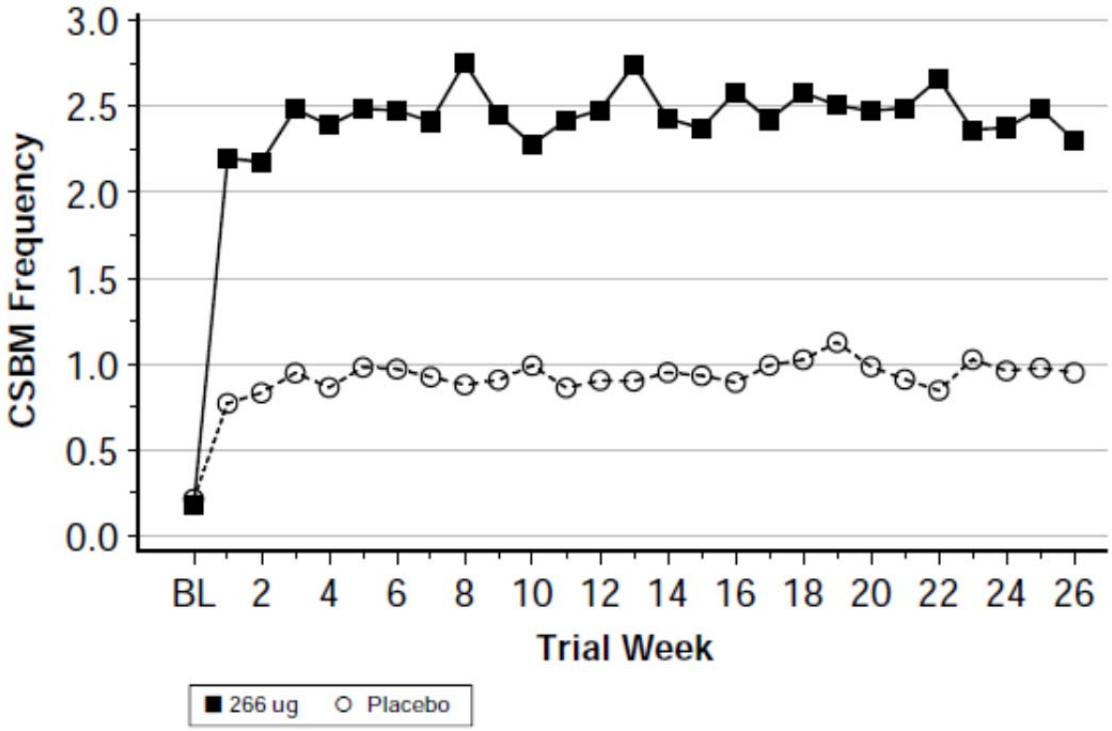
Weekly p-values < 0.0001 for all linaclotide measurements versus placebo except Week 1 (p = 0.0003); comparisons were based on an ANCOVA change from baseline model with treatment group and geographic region factors and baseline value as covariate.

ANCOVA = analysis of covariance; ITT = intent-to-treat; OC = observed cases.

Source: Table 14.4.2.5B.

Source: Clinical Study Report for study MD-31.[4]

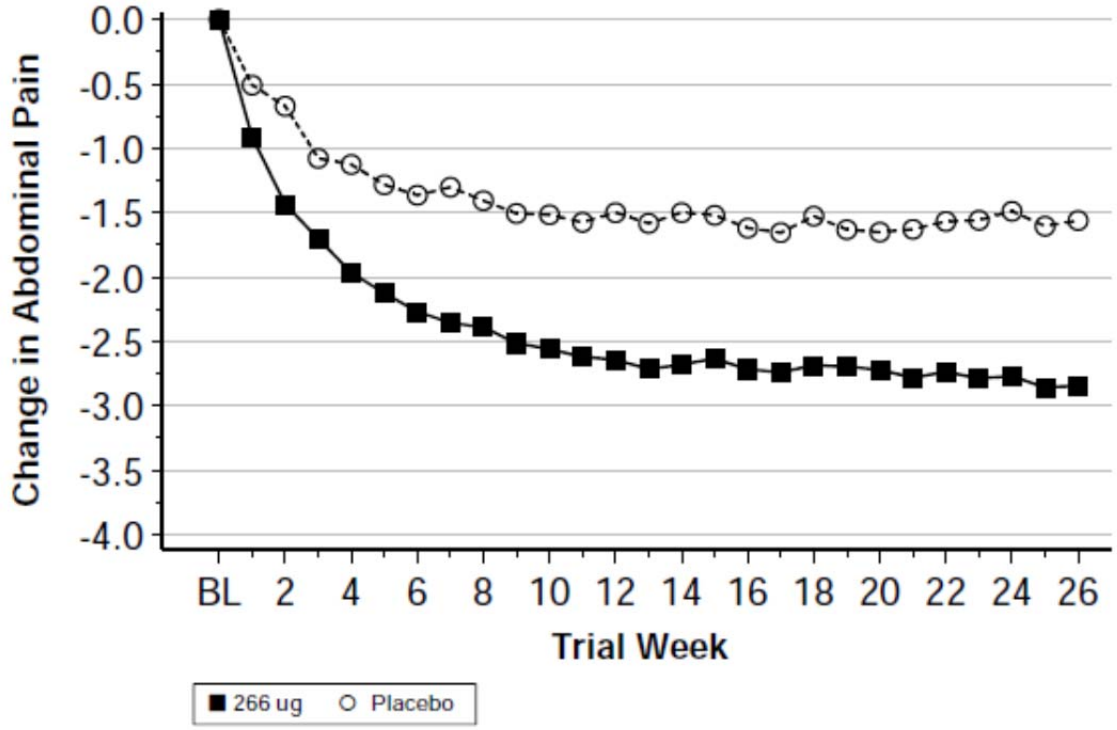
FIGURE 6: WEEKLY MEAN COMPLETE SPONTANEOUS BOWEL MOVEMENT RATE IN STUDY 302



Data Source: Section 14, Table 14.4.2.1C
Weekly $p < 0.0001$ for linaclotide versus placebo during all weeks post-baseline; comparisons were based on an ANCOVA change from baseline model, with treatment group and geographic region as factors and baseline value as a covariate.

ANCOVA = analysis of covariance; CSBM = complete spontaneous bowel movement.
Source: Clinical Study Report for study 302.[5]

FIGURE 7: WEEKLY MEAN ABDOMINAL PAIN IN STUDY 302



Data Source: Section 14, Table 14.4.2.5C
Weekly $p < 0.0001$ for linaclotide versus placebo during all weeks post-baseline; comparisons were based on an ANCOVA change from baseline model, with treatment group and geographic region as factors and baseline value as a covariate.

ANCOVA = analysis of covariance.
Source: Clinical Study Report for study 302.[5]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the characteristics, validity, limitations, and minimal clinically important differences (MCIDs) of the outcome measures used in the trials of irritable bowel syndrome with constipation (IBS-C) included in the CADTH Common Drug Review (CDR) systematic review of linaclotide:

- Composite end point APC 3+1 9/12 responders (patients who had an abdominal pain response and at least three complete spontaneous bowel movements (CSBMs) and an improvement of ≥ 1 CSBM over baseline (CSBM 3+1 response) per week in nine of 12 weeks) and its components, CSBM 3+1 9/12 responders (patients who had at least three CSBMs and an improvement of ≥ 1 CSBM over baseline per week, for at least nine of 12 weeks) and abdominal pain responders, 9/12 weeks
- Composite end point APC +1 6/12 responders (patients who had an abdominal pain response with an improvement of ≥ 1 CSBM over baseline per week in six of 12 weeks) (FDA Interim Endpoint)
- CBSM frequency
- Spontaneous bowel movement (SBM) frequency
- Stool consistency (Bristol Stool Form Scale [BSFS])
- Severity of straining
- Abdominal pain
- Abdominal discomfort
- Abdominal bloating
- Irritable Bowel Syndrome Quality of Life (IBS-QOL) measure
- EuroQol 5-Dimensions Questionnaire (EQ-5D)
- EuroQol 5-Dimensions Questionnaire Visual Analogue Scale (EQ-5D VAS)
- Work Productivity and Activity Impairment Questionnaire: Irritable Bowel Syndrome with Constipation Predominant Symptoms (WPAI:IBS-C)

Findings

The instrument, type, evidence of validity, and MCID for the above end points are summarized in Table 13, and described in greater detail in the following sections.

TABLE 13: SUMMARY OF DESCRIPTION, EVIDENCE OF VALIDITY, AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE FOR END POINTS USED IN IRRITABLE BOWEL SYNDROME WITH CONSTIPATION

Instrument	Description	Evidence of Validity	MCID/CMC	References
APC 3+1 responder, 9/12 weeks	The APC 3+1 is a composite end point assessing treatment response in IBS-C, based on patient-reported daily assessments of bowel motions and abdominal pain. Patients are classified as overall responders or non-responders. To be an overall responder, a patient has to have been a weekly responder for 9/12 treatment weeks. A weekly responder has at least 3 CSBMs in the week with an increase of at least 1 CSBM/week from baseline frequency, plus a decrease of at least 30% in the mean abdominal pain score (APC) for the week compared with	No	Not applicable to responder end point	

Instrument	Description	Evidence of Validity	MCID/CMC	References
	baseline. Abdominal pain is rated on an 11-point ordinal scale, where 0 means no abdominal pain and 10 represents very severe abdominal pain.			
CSBM 3+1 responder, 9/12 weeks	The CSBM 3+1 is one component of the above composite, measuring treatment response in bowel function for IBS-C. Patients are classified as responders and non-responders. To be an overall responder, a patient has to be a weekly responder for 9/12 treatment weeks. A weekly responder has at least 3 CSBMs with an increase of at least 1 CSBM/week from baseline frequency.	No	Not applicable	
Abdominal pain responder, 9/12 weeks	This scale measures the response of abdominal pain to treatment, and is a component of the above composite end point. Patients are classified as responders and non-responders. To be an overall responder, a patient has to be a weekly responder for 9/12 treatment weeks. A weekly responder has a decrease of at least 30% in the mean abdominal pain score (APC) for that week compared with baseline.	No	Not applicable	
APC +1 responder, 6/12 weeks	The APC +1 is a composite end point assessing treatment response in IBS-C, based on patient-reported daily assessments of bowel motions and abdominal pain. Patients are classified as responders or non-responders. To be an overall responder, a patient has to be a weekly responder for 6/12 treatment weeks. A weekly responder has an increase of at least 1 CSBM from baseline frequency, plus a decrease of at least 30% in the mean abdominal pain score (APC) for that week compared with baseline.	Yes	Not applicable	Macdougall, 2013[18]
CSBM frequency rate	The CSBM frequency rate is calculated as a mean of patient-reported data about daily BMs collected via IVRS over the period of interest.	Yes	CSBM 1.3 to 1.5 (mean), 0.5 to 1.0 (median);[18] 0.7[19] (weekly)	Macdougall, 2013;[18] Williams, 2014;[10] Camilleri, 2015[19]
SBM frequency rate	The SBM frequency rate is calculated as a mean of patient-reported data about daily BMs collected via IVRS over the period of interest.	Yes	1.9[19] (weekly)	Williams, 2014;[10] Camilleri, 2015[19]
Stool consistency (Bristol Stool Form Scale)	Stool consistency for each BM is evaluated by the patient according to the Bristol Stool Form Scale. The scale is a 7-point ordinal scale that describes the form of a BM, ranging	Yes	1.6[19]	Williams, 2014;[10] Camilleri, 2015[19]

Instrument	Description	Evidence of Validity	MCID/CMC	References
	from 1 = Separate hard lumps like nuts (difficult to pass) to 7 = Watery, no solid pieces (entirely liquid).			
Severity of straining	Severity of straining to pass each BM is reported by the patient according to a 5-point ordinal scale which ranged from 1 = not at all, to 5 = an extreme amount.	Yes	–0.8[19] (weekly)	Williams, 2014;[10] Camilleri, 2015[19]
Abdominal pain	Abdominal pain is a patient-reported assessment of worst abdominal pain in the previous 24 hours. Patients report by IVRS, using an 11-point ordinal scale ranging from 0 = no abdominal pain, to 11 = very severe abdominal pain.	Yes	25.9% to 30.4%;[18] 29.3%[19] (weekly); 29.5%[20]	Macdougall, 2013;[18] Williams, 2014;[10] Camilleri, 2015;[19] Spiegel, 2009[20]
Abdominal discomfort	Abdominal discomfort is a patient-reported assessment of worst abdominal discomfort in the previous 24 hours. Patients report by IVRS, using an 11-point ordinal scale ranging from 0 = no abdominal discomfort, to 11 = very severe abdominal discomfort.	Yes	29.3%[19] (weekly)	Williams, 2014;[10] Camilleri, 2015[19]
Bloating	Bloating is a patient-reported assessment of bloating in the previous 24 hours. Patients report by IVRS, using an 11-point ordinal scale ranging from 0 = no abdominal bloating, to 11 = very severe abdominal bloating.	Yes	20%[19] (weekly)	Williams, 2014;[10] Camilleri, 2015[19]
IBS-QOL overall score	The IBS-QOL questionnaire measures quality of life, specifically for IBS. It is a 34-item questionnaire that asks respondents to express their agreement with individual items according to a 5-point Likert scale: “not at all”, “slightly”, “moderately”, “quite a bit”, or “extremely or a great deal”. The IBS-QOL overall score is calculated by summation of the responses, and has a potential range of 34 to 100, with a higher score indicating a better quality of life. Eight sub-scales are also scored.	Yes	14 (female only, functional bowel disorder, 79% IBS)[21]	Drossman, 2007[21]
EQ-5D index	The EQ-5D is a generic quality of life instrument. Patients respond to question items that address of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Three possible levels (1, 2, or 3) for each dimension represent “no problems”, “some problems”, and “extreme problems”, respectively. The EQ-5D index is calculated from these scores using a preference-weighted scoring algorithm. On this scale, 0 represents dead, and 1.0 represents the best	Yes	Mean 0.065 (SD 0.246)	Bushnell, 2006;[22] Walters, 2005[23]

Instrument	Description	Evidence of Validity	MCID/CMC	References
	possible state of health. Negative values are permitted, representing states considered worse than dead, and are dependent upon the population in which the scoring function was derived.			
EQ-5D VAS	The EQ-5D VAS is a generic quality of life instrument. One of its components is a 20 cm vertical VAS with end points labelled 0 representing "worst imaginable health state" and 100 representing "best imaginable health state". Respondents rate their health by drawing a line from an anchor box to the point on the EQ-5D VAS which best represents their health on that day.	Yes		

APC = abdominal pain and complete spontaneous bowel movement (CSBM); APC +1 responder, 6/12 weeks = a patient who had an abdominal pain response with an improvement of ≥ 1 CSBM over baseline per week in six of 12 weeks; APC 3+1 responder, 9/12 weeks = a patient who had an abdominal pain response and at least three CSBMs and an improvement of ≥ 1 CSBM over baseline per week in nine of 12 weeks; BM = bowel movement; CMC = clinically meaningful change; CSBM = complete spontaneous bowel movement; CSBM 3+1 responder, 9/12 weeks = a patient who had at least three CSBMs and an improvement of ≥ 1 CSBM over baseline per week in nine of 12 weeks; EQ-5D = EuroQol 5-Dimensions Questionnaire; IBS = irritable bowel syndrome; IBS-C = irritable bowel syndrome with constipation; IBS-QOL = Irritable Bowel Syndrome Quality of Life measure; IVRS = interactive voice response system; MCID = minimal clinically important difference; SBM = spontaneous bowel movement; VAS = visual analogue scale.

Composite End Point APC 3+1 9/12 Responders and Components

APC 3+1 responder status is based on two patient-reported measures collected by daily interactive voice response service (IVRS): abdominal pain and CSBM. Patients are asked to rate their worst abdominal pain over the previous 24 hours on a scale of 0 to 10, where 0 represents no abdominal pain and 10 represents very severe abdominal pain. During the same call, patients are asked to report number of bowel movements, whether bowel movements were accompanied by a sense of complete evacuation, and laxative use over the previous 24 hours. A spontaneous bowel movement (SBM) is defined as a bowel movement (BM) that occurs in the absence of laxative, enema, or suppository use on either the calendar day of the BM or the calendar day before the BM. A CSBM is defined as an SBM associated with a sense of complete evacuation. From these data, responder status is determined as follows:

- *APC 3+1 9/12 responder*: A patient is classified as a weekly APC 3+1 responder if the patient has at least three CSBMs in that week with an increase of at least one CSBM from baseline frequency, plus a decrease of at least 30% in the mean abdominal pain score (APC) compared with baseline. To be an overall responder, a patient has to be a weekly responder for at least nine of the 12 weeks of the study.
- *CSBM 3+1 9/12 responder*: A patient is classified as a weekly CBSM 3+1 responder if the patient has at least three CSBMs in that week with an increase of at least one CSBM from baseline frequency. To be an overall responder, the patient has to be a weekly responder for at least nine of the 12 weeks of the study.
- *Abdominal pain responder, 9/12*: A patient is classified as a weekly abdominal pain responder if the patient has a decrease of at least 30% in the mean abdominal pain score compared with baseline. To be an overall responder, the patient has to be a weekly responder for at least nine of the 12 weeks of the study.

There are no reports validating this specific end point or of estimating its MCID. The FDA end point, which uses the same changes from baseline for weekly responders, has been validated as described in the next section.

Composite End Point APC +1 6/12 Responder (FDA Responder Endpoint)
APC +1 responder status is based on two patient-reported measures collected by daily IVRS, abdominal pain, and CSBM, as collected and defined in the previous section. From these data, responder status is determined as follows:

- *APC +1 6/12 responder:* A patient is classified as a weekly APC +1 responder if the patient has an increase of at least one CSBM from baseline frequency, plus a decrease of at least 30% in the mean abdominal pain score (APC) compared with baseline. To be an overall responder, the patient has to be a weekly responder for at least six of the 12 weeks of the study.

This was proposed as an interim end point by the FDA in a 2009 conference given by the Rome Foundation and published in its final form in 2012.[24] It has been evaluated using the data from the two linaclotide phase 3 clinical trials against symptom-specific outcome measures collected in the same trial.[18,19] A total of 1,062 patients were included.

Concurrent validity: Within-patient agreement between the established binary global end point of Adequate Relief and the FDA weekly responder criteria averaged over 12 weeks is 70% in the linaclotide group and 76% in the placebo group.[19]

Sensitivity, specificity, and accuracy of the APC +1 6/12 responder end point were calculated against a reference standard created from a dichotomized mean from symptom-specific Patient Rating of Change Questions (PRCQs) for Abdominal Pain Relief and CSBM Frequency Improvement.[18] Responders had to have a mean of 3.0 or less in both Abdominal Pain Relief and CSBM Frequency Improvement over 12 weeks, which corresponded to somewhat, considerably, or completely improved/relieved. Sensitivity, specificity, and accuracy for APC +1 6/12 were 60.7%, 93.5%, and 82%, respectively.[18] If the threshold for weeks of response is chosen as 9/12 weeks rather than 6/12 weeks, as in the APC 3+1 9/12 end point, sensitivity decreased to 37.8%, and specificity and accuracy were 98.7%, and 77.3%, respectively.[18]

MCID was estimated for the components of the composite end point by an anchor-based method using five different scales as anchors: symptom-specific PRCQs for Abdominal Pain Relief and CSBM Frequency Improvement, global PRCQ Degree of Relief of IBS, and IBS and Constipation Severity Questions.[18] The MCID was calculated as the average over all weeks that the patients met the anchor criterion. The MCID for abdominal pain ranged from 25.8% (anchor: symptom-specific measure of weekly Abdominal Pain Relief) to 30.4% (anchor: IBS symptom severity). The MCID for CSBM ranged from a mean 1.3 to 1.5, and a median 0.5 to 1.0 (anchor: symptom-specific measure of weekly CSBM frequency change).[18]

Using the same dataset and the patient-reported global outcome of Adequate Relief as an anchor, a clinically meaningful change (CMC) of 29.3% was estimated for abdominal pain, and a CMC of 0.7 was estimated for CSBMs/week.[19]

In an evaluation of a 10-point patient-reported numerical rating scale for abdominal pain, using data from a longitudinal study of female IBS patients, Spiegel et al. 2009 found a MCID of 2.2 points, corresponding to a 29.5% MCID reduction over time.[20]

Complete Spontaneous Bowel Movement and Spontaneous Bowel Movement Frequency Rate
Both the CSBM and SBM frequency rates were calculated from daily patient reports of BMs during the previous 24 hours. An SBM is defined as a BM that occurs in the absence of laxative, enema, or suppository use on either the calendar day of the BM or the calendar day before the BM. A CSBM is defined as an SBM associated with a sense of complete evacuation.

Reliability, construct validity, responsiveness, and MCID were determined for a dataset derived from LIN-MD-31 and MCP-103-302, involving 1,602 patients.[10,19]

Test-retest **reliability** was tested by the ICC (intra-class correlation coefficient) for measurements taken during the last two weeks of treatment, when symptoms were expected to be stable. The ICC was 0.86 for both measures, above the recommended threshold of 0.70.[10] **Construct validity** was assessed by inter-item correlations between the various severity measures, with greater correlations expected between pairs of measures of abdominal symptoms than of abdominal symptoms with bowel symptoms. CSBM frequency and SBM frequency correlated strongly with patient-reported constipation severity, and with straining.[10] **Responsiveness** was tested by comparing mean results for responders according to the FDA Interim Endpoint with non-responders. Both comparisons were statistically significant, with standardized effect sizes (based on the standard deviation [SD] of change in the non-responder group) of 2.1 and 1.0 for CSBM frequency and SBM frequency, respectively.[10]

In a separate analysis with the same dataset, the BM frequency measures showed moderate correlation with the established binary global end point of Adequate Relief: 0.38 for CSBMs/week, and 0.34 for SBMs/week.[19]

MCID: Using the same dataset, with the patient-reported global outcome of Adequate Relief as an anchor, CMCs of 0.7 and 1.9 were estimated for CSBMs/week and SBMs/week, respectively.[19]

Bristol Stool Form Scale (Stool Consistency)
During the daily IVRS, patients self-reported stool consistency for individual BMs according to the BSFS, which is a 7-point ordinal scale for describing the consistency of a BM:
1 = separate hard lumps like nuts (difficult to pass)
2 = sausage-shaped but lumpy
3 = like a sausage but with cracks on surface
4 = like a sausage or snake, smooth and soft
5 = soft blobs with clear-cut edges (passed easily)
6 = fluffy pieces with ragged edges, a mushy stool
7 = watery, no solid pieces (entirely liquid).

The BSFS has been correlated with the surrogate measure of colonic transit time in irritable bowel syndrome (IBS) in patients participating in a treatment trial.[25]

Reliability, construct validity, responsiveness, and MCID were determined for a dataset derived from LIN-MD-31 and MCP-103-302, involving 1,602 patients.[10,19]

Reliability was tested by the ICC for measurements taken during the last two weeks of treatment, when symptoms were expected to be stable. The ICC was 0.79, above the recommended threshold of 0.70.[10]

Construct validity was assessed by calculation of inter-item correlations between the various severity measures. Stool consistency correlated with straining (–0.62) and patient-reported constipation severity (–0.49).[10] **Responsiveness** was tested by comparing mean results for responders according to the FDA Interim Endpoint with non-responders. The comparison was statistically significant, although the effect size was considered moderate (0.6).[10]

In a separate analysis with the same dataset, correlation with the established binary global end point of Adequate Relief was moderate at 0.32 (the threshold is 0.3).[19]

MCID: Using the same dataset, with the patient-reported global outcome of Adequate Relief as an anchor, a CMC of 1.6 was reported for stool consistency.[19]

Severity of Straining

During the daily IVRS, patients reported severity of straining associated with passing each BM according to a 5-point ordinal scale: 1 = not at all; 2 = a little bit; 3 = a moderate amount; 4 = a great deal; 5 = an extreme amount.

Construct validity, responsiveness, and MCID for severity of straining were determined for a dataset derived from LIN-MD-31 and MCP-103-302, involving 1,602 patients.[10]

Construct validity was assessed by calculation of inter-item correlations between the various severity measures. Straining correlated strongly with IBS severity (0.71) and patient-reported constipation severity (0.67).[10] **Responsiveness** was tested by comparing mean results for responders according to the FDA Interim Endpoint with non-responders. The comparison was statistically significant, with a standardized effect size of –1.0.[10]

MCID: Using the same dataset, with the patient-reported global outcome of Adequate Relief as an anchor, a CMC of –0.8 was reported for severity of straining.[19]

Abdominal Pain, Abdominal Discomfort, and Bloating

During the daily IVRS, patients self-reported abdominal symptoms of Abdominal Pain, Abdominal Discomfort and Abdominal Bloating. Although IBS patient-reported outcome measures have frequently assessed pain or discomfort, patient data suggests they are distinctive experiences.[24] For each scale, patients were asked to rate their symptoms at their worst over the previous 24 hours on a scale of 0 to 10, where 0 represents none and 10 represents very severe.

Reliability, construct validity, responsiveness, and MCID were determined for a dataset derived from LIN-MD-31 and MCP-103-302.[10,19]

Test-retest reliability was tested by calculating the ICC for measurements taken during the last 2 weeks of treatment, when symptoms were expected to be stable. For all scales, this was 0.95.[10] **Construct validity** was assessed by inter-item correlations between the various severity measures, with greater correlations expected between pairs of measures of abdominal symptoms than of abdominal symptoms with bowel symptoms. Abdominal pain was highly correlated with abdominal discomfort (0.93) and abdominal discomfort with abdominal bloating (0.90). **Responsiveness** was tested by comparing mean results for responders according to the FDA Interim Endpoint with non-responders. The comparisons were significant in all cases, with standardized effect sizes (based on the SD of change in the non-responder group) of –1.6 to –1.8.

In a separate analysis of the same dataset, there was a large correlation with the established binary global end point of Adequate Relief for each of the three scales, with correlation coefficients of 0.50 to 0.54.[19]

MCID: The derivation of the MCID for abdominal pain is described above. Using data from LIN-MD-31 and MCP-103-302, with the patient-reported global outcome of Adequate Relief as an anchor, CMCs of 29.3% and 20.0% were calculated for Abdominal Discomfort and Abdominal Bloating, respectively.[19]

Irritable Bowel Syndrome Quality of Life Assessment

The IBS-QOL measure is a 34-item questionnaire that assesses domains of symptoms, functional status, perceived quality of life, and social disability.[15] Respondents are asked to express their agreement with individual items according to a 5-point Likert scale: "not at all", "slightly", "moderately", "quite a bit", or "extremely or a great deal". The IBS-QOL overall score is calculated by summation, and has a potential range of 34 to 100, with a higher score indicating a better quality of life. Eight individual sub-scales address the domains of dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual, and relationships. The IBS-QOL was developed by standardized psychometric measures involving a literature search, physician and patient interviews, and a cultural adaptation process to enable its use in Europe as well as the US. The content validity has been confirmed by physician and patient groups in the US and Europe.[15] There were no significant differences in results between electronic data capture and paper questionnaires for the IBS-QOL for 72 patients with IBS (25% with constipation predominant and 42% with alternating constipation and diarrhea).[26]

The internal consistency, reproducibility, construct reliability, and discriminant viability was determined by a two-centre psychometric evaluation study of 169 patients recruited through advertisements or through gastroenterology clinics or physicians' offices.[15] The average patient age was 39 years, 89% were female, 22% had predominately constipation, and 60% had IBS with mixed constipation and diarrhea. Patients had to complete a self-administered questionnaire consisting of the IBS-QOL and disease-specific and quality of life measures, Symptom Frequency and Bothersomeness, Functional Bowel Disorder Severity Index (FBDSI), Medical Outcome Study Short Form (Short Form [36] Health Survey [SF-36]), Psychological General Well-Being Scale (PGWB), Symptom Check List (SCL-90-R), and Work-Loss days. A random subset underwent a retest 14 days later, where they completed a second IBS-QOL questionnaire and rated change in their quality of life over the previous two weeks.[15]

The **internal consistency**, calculated by Cronbach's alpha (a function of the number of test items and the average intercorrelation between them) was 0.95 overall.[15] The eight individual sub-scales had values for ICC ranging from 0.74 to 0.92, with the exception of relationships: 0.65. **Reproducibility**, assessed by the ICC, was 0.86 for those patients who reported no change in their bowel symptoms, with values for sub-scales ranging from 0.76 to 0.89, except for relationships: 0.65.[15] **Construct validity** was assessed by calculating the strength of association between the global IBS-QOL and the SF-36, PGWB, and SCL-90-R, global score and sub-scales, where indicated. No exceptionally strong correlations were noted. Correlations with the SF-36 were strongest for bodily pain and physical functioning. Correlations for the PGWB were confirmed for the total score and health worry and concerns. **Discriminant validity** was tested by comparing the IBS-QOL with the Symptoms Frequency and Bothersome Index scores, the FBDSI, and a patient-reported measure of severity. Greater severity by these measures was correlated with poorer quality of life.[15] **Responsiveness** was assessed in a separate cohort of 402 female patients with functional bowel disorder, of whom 317 had IBS.[21] The IBS-QOL scores did not differ between types of functional bowel disorder, or between subtypes of IBS. When compared with response according to

treatment satisfaction, standardized scores for respondents were significantly different to non-respondents.[21] The authors concluded that the IBS-QOL had been shown to be adequately responsive.

The MCID for the IBS-QOL was 14, calculated using the SD at baseline for the same cohort of 402 female patients with functional bowel disorder.[21]

EuroQol 5-Dimensions Questionnaire

The EQ-5D is a generic quality of life (QoL) instrument that may be applied to a wide range of health conditions and treatments.[27] The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged 12 years or older) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing "no problems", "some problems", and "extreme problems", respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[27] The second part is a 20 cm visual analogue scale (EQ-5D VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state". Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their health on that day. Hence, the EQ-5D produces three types of data for each respondent:

- A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
- A population preference-weighted health index score based on the descriptive system (EQ-5D index)
- A self-reported assessment of health status based on the EQ VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., –0.59 for the UK algorithm and –0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health", respectively. Reported clinically important differences (CIDs) for this scale have ranged from 0.033 to 0.074.[28]

The construct validity, discriminant validity, and responsiveness of the EQ-5D in patients with IBS was assessed using data from studies of symptoms, quality of life, and resource use by patients with IBS in the UK, Spain, and Germany.[22] A total of 1,060 patients were involved: 161 and 297 in the two UK studies, 503 in the study in Spain, and 100 in the study in Germany. The mean ages for patients in the four studies ranged from 42.7 years to 53.8 years, and the proportion of females ranged from 75.9% to 86.3%. There were no significant differences in results between electronic data capture and paper questionnaires for the EQ-5D for 72 patients with IBS (25% with constipation predominant and 42% with alternating constipation and diarrhea).[26]

Construct validity was shown in the two UK studies by the strong correlations (Spearman correlation coefficient 0.5 or greater) between the EQ-5D mobility dimension and the SF-36 physical function domain (–0.70 and –0.71), the EQ-5D pain/discomfort dimension and the SF-36 bodily pain domain (–0.63 and –0.66), the ED-5D anxiety/depression dimension and the SF-36 mental health domain (–0.65 and –0.60).[22] The EQ-5D VAS was strongly correlated with the SF-36 general health domain (–0.71 and –

0.67). Correlations between the dimensions of the EQ-5D and the IBS-QOL, measured for all four studies, were moderate for most dimensions, and lower but still significant for mobility and self-care. The stronger correlations between the two generic instruments were as expected. **Discriminant validity** was shown in the larger UK study by the significant inverse relationship between the EQ-5D VAS and the VAS-ADP (abdominal pain 0–100 visual analogue scale) divided into tertiles (F = 22.1, *P* < 0.001).[22] Similar associations were found for the patient's assessment of IBS pain in the German study, and IBS severity in the Spanish study. The EQ-5D index discriminated between tertiles of pain severity as measured by the VAS-ADP (F = 29.2, *P* < 0.001).[22] **Responsiveness** of the EQ-5D VAS and the EQ-5D index score as global measures of change was shown when compared with improvement/worsening/no change in physician-reported VAS-ADP and Clinician's Global Assessment of Change (CGA) over one year follow-up. For patients who improved, the calculated effect size statistic (mean change score divided by the standard deviation of baseline score) for EQ-5D VAS was 0.64 for VAS-ADP and 0.48 for CGA. For the same patients for EQ-5D index it was 0.33 and 0.29 for VAS-ADP and CGA, respectively.[22]

MCID: From a longitudinal study with change from follow-up to six months, the mean MCID in the EQ-5D index score for IBS-C patients in the intervention group who reported some change (either for the better or for the worse) was 0.065.[23] The magnitude differed depending upon the direction of change (somewhat better: 0.002; somewhat worse: 0.101), but the difference was not statistically significant.

Work Productivity and Activity Impairment Questionnaire: Irritable Bowel Syndrome with Constipation Predominant Symptoms

The Work Productivity and Activity Impairment (WPAI) questionnaire measures the impact of symptoms of a specific health condition upon work and other activities during the previous seven days.[16] The WPAI:IBS-C used in this study differs from the standard Work Productivity and Activity Impairment: Irritable Bowel Syndrome (WPAI:IBS) by removal of mention of diarrhea as a symptom of IBS. The WPAI:IBS-C consists of six questions: employment status (employed or not employed); hours at work missed because of IBS, hours at work missed because of other reasons; hours actually worked; degree IBS affected productivity while working (VAS from 0 to 10) and the degree IBS affected regular activities (VAS from 0 to 10). Patients who are employed answer all questions, while those who are not employed answer the first and last. From these, four measures are calculated. Scores are expressed as percentage of impairment/productivity loss, with higher scores indicating greater impairment.[16]

- WPAI:IBS-C Absenteeism: work time missed
- WPAI:IBS-C Presenteeism: productivity at work
- WPAI:IBC-C Productivity Loss: absenteeism plus presenteeism
- WPAI:IBS-C Daily Activity Impairment

Construct validity, discriminative validity, and reproducibility for the WPAI:IBS were assessed in a sample of 135 patients from five US sites.[16] Patients had to meet the Rome II criteria for IBS. Patients' mean age was 45.5 years, 91% were female, 27% had predominately constipation, and 39% had mixed constipation and diarrhea. All but two were currently employed; those not employed were excluded from calculation of work-related measures. Patients completed a questionnaire consisting of demographics and disease severity, the WPAI:IBS, Work Limitations Questionnaire (WLQ), Debriefing and Dimensions of Daily Activities (DDAI), and a retrospective diary. To assess the effect of the order of administration, patients were randomized to receive the WPAI:IBS and DDAI or the WLQ first. There were no significant differences in results between electronic data capture and paper questionnaires for the WPAI:IBS for 72 patients with IBS (25% with constipation predominant and 42% with alternating constipation and diarrhea).[26] However, the authors noted that only a minority of this cohort was stably employed.

For **construct validity**, the seven-day retrospective assessments of the WPAI:IBS showed good correlation with work absences and work impairment as recorded in a daily diary.[16] There was, however, no independent validation of patient report. For **discriminant validity**, symptom severity levels (none/mild, moderate, severe, no symptoms) were a significant predictor of all measures except missed work time (P = 0.06).[16] Symptom severity (10-point VAS) and symptom distress were significant predictors of all WPAI:IBS measures. **Reproducibility** was measured by correlation between responses to the WPAI:IBS and subsequent review and debriefing, with a correlation coefficient of 0.97 to 0.99, and exact agreement from 91% to 95%.[16]

Conclusion

Assessment of IBS, as a functional bowel disorder, relies on patient-reported outcomes. For drug development, both the FDA and the European Medicines Agency have released guidance documents with recommended end points. This was proposed as an interim end point by the FDA in a 2009 conference given by the Rome Foundation and published in its final form in 2012.[24] Published evaluations of the FDA-recommended end points have relied on the phase 2 and phase 3 pivotal trials of linaclotide that are the subject of this review (study MD-31 and study-302). Published evaluations of other end points have been conducted using patient cohorts that included all types of IBS. Quoted MCIDs are based on within-group differences rather than between-group differences.

The APC 3+1 9/12 is a composite end point assessing treatment response in IBS-C, based on patient-reported daily assessments of bowel motions and abdominal pain. APC +1 9/12 has yet to be validated, and as a response end point, there is no MCID.

The CSBM 3+1 9/12 is one component of the above composite end point. CSBM 3+1 9/12 has yet to be validated, and as a response end point, there is no MCID.

Abdominal pain responder, 9/12 weeks is the second component of the above composite end point. The abdominal pain responder, over 9/12 weeks has yet to be validated, but the MCID for weekly change in abdominal pain in IBS has been estimated as 25.9% to 30.4%.

The APC +1 6/12 is a composite end point assessing treatment response in IBS-C, based on patient-reported daily assessments of bowel motions and abdominal pain. APC +1 6/12 has been evaluated in IBS-C using the study MD-31 and study-302 datasets. As a response end point, there is no MCID.

The CSBM frequency rate is calculated as a mean of patient-reported data about daily BMs collected via IVRS over the period of interest. It has been validated against other IBS-related scales for IBS-C using the study-MD-31 and study-302 datasets, and MCIDs of 0.7/week to 1.5/week have been estimated.

The SBM frequency rate is calculated as a mean of patient-reported data about daily BMs collected via IVRS over the period of interest. It has been validated against other IBS-related scales for IBS-C using the study-MD-31 and study-302 datasets, with an estimated MCID of 1.9/week.

The BSFS is a 7-point patient-reported scale for measuring stool consistency from hard and difficult to pass (1) to entirely liquid (7). It has been validated against other IBS-related scales for IBS-C using the study MD-31 and study-302 datasets, with a MCID of 1.6.

Severity of straining is a 5-point patient-reported scale for measuring effort associated with passing a BM, ranging from not at all (1) to an extreme amount (5). It has been validated for IBS-C using the study MD-31 and study-302 datasets, with a MCID of –0.8.

Abdominal pain is an 11-point patient-reported scale for measuring abdominal pain, used in the above composite end points. It has been validated for IBS-C using the LIN-MD-31 and MCP-103-302 dataset, and in other datasets, with estimated MCIDs ranging from 25.9% to 32.4%.

Abdominal discomfort is an 11-point patient-reported scale for measuring abdominal discomfort. It has been validated for IBS-C using the study MD-31 and study-302 datasets, with an estimated MCID of 29.3%.

Abdominal bloating is an 11-point patient-reported scale for measuring bloating. It has been validated in IBS-C using the study MD-31 and study -302 trials datasets, with an estimated MCID of 20%.

The IBS-QOL questionnaire measures quality of life specifically for IBS. It has been validated in a cohort of women with functional bowel disease (79% IBS) and an MCID of 14 has been estimated.

The EQ-5D is a generic quality of life instrument that produces a single score index and a VAS. Both have been validated in numerous conditions including IBS, with a mixed IBS cohort. An MCID of 0.065 has been estimated for the EQ-5D index for IBS.

The WPAI:IBS-C measures the impact of symptoms of IBS on work and other activities. It was derived from the WPAI:IBS, which has been validated in a mixed IBS cohort. Since it is an economic measure, no MCID has been calculated.

APPENDIX 6: SUMMARY OF OTHER STUDIES

1. Objective

To summarize additional relevant trials that do not meet the selection criteria for inclusion into the systematic review such as open-label extension phases of trials included in the systematic review.

2. Findings

Reports of two multi-centre, open-label, extension safety studies (LIN-MD-02 and MCP-103-305) for linaclotide in irritable bowel syndrome with constipation (IBS-C) and chronic constipation were supplied by the manufacturer. No other extension studies were identified in literature review. Only the results for IBS-C are discussed in this appendix.

To qualify for LIN-MD-02 or MCP-103-305, patients had to have completed one or more of the phase 2 or phase 3 registration studies, or to have entered and completed phase 3 pre-treatment but failed to satisfy one of more specific inclusion or exclusion criteria for randomization. These criteria concerned symptom severity and compliance with data collection. Additional inclusion/exclusion criteria depended upon which trials patients had previously entered. Details of the key inclusion and exclusion criteria are given in Table 14.

TABLE 14: TABLE OF INCLUDED STUDIES

		LIN-MD-02	MCP-103-305
DESIGNS & POPULATIONS	Study design	Open-label extension study	Open-label extension study
	Locations	118 centres: Canada, US	116 centres: US
	Study period	October 31, 2008 to January 12, 2012	September 15, 2008 to March 9, 2012
	Included (N)	[redacted] total 1,554)	[redacted] total 1,725)
	Inclusion criteria	Depended on patient group: • Phase 3 RI patients: Completed pre-treatment but did not meet specific criteria for randomization into LIN-MD-31 (IBS-C) or LIN-MD-01 (chronic constipation). • Phase 3 completed patients (RO): completed LIN-MD-31 or LIN-MD-01. • Phase 2 completed patients (RO): completed any linaclotide phase 2 study (MCP-103-004, MCP-103-005, MCP-103-201, or MCP-103-202). *For the sake of brevity, all subsequent references to LIN-MD-01 and patients with chronic constipation have been omitted.* **Phase 3 RI patients** *Did not meet one or more of the following key inclusion criteria for LIN-MD-31:* • Average score for abdominal pain at its worst of 3.0 or higher on 11-point	Depended on patient group: • Phase 3 RI patients: Completed pre-treatment but did not meet specific criteria for randomization into MCP-103-302 (IBS-C) or MCP-103-303 (chronic constipation). • Phase 3 completed patients (RO): completed MCP-103-302 or MCP-103-303. • Phase 2 completed patients (RO): completed any linaclotide phase 2 study (MCP-103-004, MCP-103-005, MCP-103-201, or MCP-103-202). *For the sake of brevity, all subsequent references to MCP-103-303 and patients with chronic constipation have been omitted.* **Phase 3 RI patients** *Did not meet one or more of the following key inclusion criteria for MCP-103-302:* • Average score for abdominal pain at its worst of 3.0 or higher on 11-point numeric rating scale during the 14 calendar days prior to start of treatment period.

		LIN-MD-02	MCP-103-305
		numeric rating scale during the 14 calendar days prior to start of treatment period. • Fewer than 3 CSBMs and 5 or fewer SBMs per week during the 14 days prior to start of treatment period. ***Or*** *did not meet one or more the following key exclusion criteria for LIN-MD-31:* • BSFS score of 6 (loose, mushy stools) with more than 1 SBM or a BSFS score of 7 (watery stools) with any SBM during the 14 days prior to start of treatment period. • Used rescue medication or any other laxative, enema, or suppository on day of or day before start of treatment period. • Used a prohibited medication during the pre-treatment period **Phase 3 completed patients (RO)** • Completed LIN-MD-31, with adequate compliance. **Phase 2 completed patients (RO)** • Met the Rome II criteria for IBS. • Reported fewer than 3 BMs per week and 1 or more of the following symptoms for at least 12 weeks: o Straining during more than 25% of BMs o Lumpy or hard stools during more than 25% of BMs o Sensation of incomplete evacuation during more than 25% of BMs.	• Fewer than 3 CSBMs and 5 or fewer SBMs per week during the 14 days prior to start of treatment period. ***Or*** *did not meet one or more the following key exclusion criteria for MCP-103-302:* • BSFS score of 6 (loose, mushy stools) with more than 1 SBM or a BSFS score of 7 (watery stools) with any SBM during the 14 days prior to start of treatment period. • Used rescue medication or any other laxative, enema, or suppository on day of or day before start of treatment period. • Used a prohibited medication during the pre-treatment period. **Phase 3 completed patients (RO)** • Completed MCP-103-302, with adequate compliance. **Phase 2 completed patients (RO)** • Met the Rome II criteria for IBS. • Reported fewer than 3 BMs per week and 1 or more of the following symptoms for at least 12 weeks: o Straining during more than 25% of BMs o Lumpy or hard stools during more than 25% of BMs o Sensation of incomplete evacuation during more than 25% of BMs.
	Exclusion criteria	Depended on patient group (see above). **Phase 3 RI patients** • Average of more than 1.0 SBM for each reported day of the pre-treatment period of LIN-MD-31. • BSFS score of 6 or 7 in the absence of any laxative, enema, or suppository with more than 25% of SBMs during the pre-treatment period of LIN-MD-31.	Depended on patient group (see above). **Phase 3 RI patients** • Average of more than 1.0 SBM for each reported day of the pre-treatment period of MCP-103-302. • BSFS score of 6 or 7 in the absence of any laxative, enema, or suppository with more than 25% of SBMs during the pre-treatment period of MCP-103-302. **Phase 2 completed patients** • Phase 2 completed patients had to meet

		LIN-MD-02	MCP-103-305
		Phase 2 completed patients • Phase 2 completed patients had to meet exclusion criteria similar to those used in LIN-MD-31 to exclude major gastrointestinal diseases, history of gastrointestinal surgery, or other major morbidity.	exclusion criteria similar to those used in MCP-103-302 studies to exclude other major gastrointestinal diseases or history of gastrointestinal surgery.
DRUGS	Intervention	Linaclotide 290 mcg daily	Linaclotide 290 mcg daily
DURATION	Duration	Duration of administration 78 weeks (18 months)	Duration of administration 78 weeks (18 months)
OUTCOMES	Safety end points	AEs (graded for severity, seriousness, and relationship to treatment). Clinical laboratory determinations (hematology, chemistry, urinalysis). Vital signs, ECG, physical examination.	AEs (graded for severity, seriousness, and relationship to treatment). Clinical laboratory determinations (hematology, chemistry, urinalysis). Vital signs, ECG, physical examination.
	Health outcomes	Assessment of treatment satisfaction.	Assessment of treatment satisfaction.

AE = adverse event; BM = bowel movement; BSFS = Bristol Stool Form Scale; CSBM = complete spontaneous bowel movement; ECG = electrocardiogram; IBS = irritable bowel syndrome; IBS-C = irritable bowel syndrome with constipation; RI = randomization ineligible; RO = rollover; SBM = spontaneous bowel movement.
Source: Clinical Study Reports for study LIN-MD-02[29] and MCP-103-305.[30]

All patients in both studies started at 290 mcg linaclotide daily. In the event of tolerability concerns, the dose could be suspended and then resumed either at 290 mcg or 145 mcg per day, at the investigator's discretion. Further dose adjustments were then allowed within the range of 145 mcg per day and 290 mcg per day, at the investigator's discretion.

Dosing continued for 78 weeks (18 months), [redacted] The safety populations included all patients who received at least one dose of linaclotide.

[redacted]

Baseline characteristics of the IBS-C patient subgroup are summarized in Table 15. The analysis made a distinction between randomization ineligible (RI) patients who did not qualify to enter the phase 3 studies after pre-treatment, and rollover (RO) patients who completed a phase 2 or phase 3 study. Only demographic baseline characteristics are available since baseline disease characteristics were not tabulated for the sample in the extension studies; this precludes any comparison of average symptom severity for RI and RO cohorts. [redacted]

[redacted]

TABLE 15: SUMMARY OF BASELINE CHARACTERISTICS

	LIN-MD-02			MCP-103-305		
	RI (N = 488)	RO (N = 544)	Total (N = 1,032)	RI (N = 469)	RO (N = 650)	Total (N = 1,119)
Mean (SD) age, years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

RI = randomization ineligible; RO = rollover; SD = standard deviation.
Source: Clinical Study Reports for study LIN-MD-02[29] and MCP-103-305.[30]

Important concomitant medications used by more than 10% of patients at any time during the study are summarized in Table 16. [redacted]

TABLE 16: COMMON CONCOMITANT MEDICATIONS USED AT ANY TIME DURING THE STUDY

	LIN-MD-02			MCP-103-305		
	RI (N = 488)	RO (N = 544)	Total (N = 1,032)	RI (N = 469)	RO (N = 650)	Total (N = 1,119)
Selective serotonin reuptake inhibitors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Benzodiazepine derivatives	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other antidepressants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thyroid hormones	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natural opium alkaloids	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

RI = randomization ineligible; RO = rollover.
Source: Clinical Study Reports for study LIN-MD-02[29] and MCP-103-305.[30]

PATIENT DISPOSITION FOR THE IBS-C PATIENT SUBGROUP IS SUMMARIZED IN

Table 17. [redacted]

TABLE 17: SUMMARY OF PATIENT DISPOSITION

	LIN-MD-02			MCP-103-305		
	RI (N = 488)	**RO (N = 544)**	**Total (N = 1,032)**	**RI (N = 469)**	**RO (N = 650)**	**Total (N = 1,119)**
Completed study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol violation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insufficient therapeutic response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Did not meet inclusion/exclusion criteria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study terminated by sponsor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NR = not reported; RI = randomization ineligible; RO = rollover.
Source: Clinical Study Reports for study LIN-MD-02[29] and MCP-103-305.[30]

Harms for the IBS-C patient subgroup are summarized in Table 18. [redacted]

[redacted]

[redacted]

[redacted]

TABLE 18: SUMMARY OF HARMS

	LIN-MD-02			MCP-103-305		
	RI (N = 488)	RO (N = 544)	Total (N = 1,032)	RI (N = 469)	RO (N = 650)	Total (N = 1,119)
Adverse Events						
Patients with > 0 AEs n (%)	[redacted]					
Most common AEs[a]						
Serious Adverse Events						
Patients with > 0 SAEs, n (%)	[redacted]					
Most common SAEs[b]						
Non-cardiac chest pain	[redacted]					
Angina pectoris	[redacted]					
Breast cancer	[redacted]			[redacted]		
Osteoarthritis				[redacted]		
Cholelithiasis				[redacted]		
WDAEs						
WDAEs, N (%)	[redacted]					
Deaths						
Deaths, n (%)	[redacted]			[redacted]		
Notable harms						
Diarrhea	[redacted]					
Abdominal pain	[redacted]					
Nausea	[redacted]					
Abdominal distention	[redacted]					
Flatulence	[redacted]					
Gastroenteritis viral	[redacted]					
Defaecation urgency	[redacted]					
Vomiting	[redacted]					

AE = adverse event; RI = randomization ineligible; RO = rollover; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] > 2% of patients.
[b] > Two patients.
[c] One additional patient died > 30 days after the last dose of study drug.
[d] One additional patient had breast cancer, stage I, also reported as an SAE.
Source: Clinical Study Reports for study LIN-MD-02[29] and MCP-103-305.[30]

The longer-term treatment duration in the open-label extension studies LIN-MD-02 and MCP-103-305 is generally more reflective of the management of IBS-C in clinical practice, where treatment is likely to be long-term, rather than the 12- or 26-week treatment duration in the included RCTs. In addition, the extension studies allowed for dose interruption and dose reduction in response to tolerability concerns. The main limitations of the extension studies arise from their non-randomized, open-label design and lack of a comparator group. It follows that the lack of a comparator group precludes being able to differentiate between gastrointestinal symptoms arising from abdominal and bowel-related treatment-related adverse events from the fluctuation in disease symptoms typical of IBS.

Another criticism of the open-label extension studies is that they include a pre-selected population of patients who have completed a prior study and therefore demonstrated tolerance for the drug. Both LIN-MD-02 and MCP-103-305 include a second group of patients drawn from those who were screened and considered eligible for the RCTs, but who did not meet the symptom severity criteria during the run-in phase. Given the fluctuating nature of IBS symptoms, they may or may not represent a less severe population (baseline data are not available). They do, however, represent patients without prior exposure to linaclotide, and therefore should present a more typical tolerability profile. They were more likely to discontinue due to adverse events than those in the RCTs, particularly due to diarrhea.

3. Summary

Reports of two multi-centre, open-label, extension safety studies (LIN-MD-02 and MCP-103-305) were supplied by the manufacturer. No other extension studies were identified in the literature review.

To qualify for LIN-MD-02 or MCP-103-305, patients had to have completed one or more of the phase 2 or phase 3 registration studies, or to have entered and completed phase 3 pre-treatment but failed to satisfy one of more specific inclusion or exclusion criteria for randomization. These criteria concerned symptom severity and compliance with data collection.

All IBS-C patients in both studies started at 290 mcg linaclotide daily, with adjustments allowed for tolerability. Dosing continued for up to 78 weeks, [redacted]

[redacted]

[redacted] Overall, there were no unexpected safety signals.

REFERENCES

1. Wald A. Treatment of irritable bowel syndrome in adults. 2014 [cited 2015 Apr 15]. In: UpToDate [Internet]. Waltham (MA): UpToDate; c2005 - . Available from: www.uptodate.com Subscription required.
2. Weinberg DS, Smalley W, Heidelbaugh JJ, Sultan S, Amercian Gastroenterological Association. American Gastroenterological Association Institute Guideline on the pharmacological management of irritable bowel syndrome. Gastroenterology. 2014 Nov;147(5):1146-8.
3. CDR submission: Constella® (linaclotide), 145 mcg and 290 mcg capsules. Company: Actavis Specialty Pharmaceuticals [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Actavis Specialty Pharmaceuticals; 2014 Dec 16.
4. Clinical Study Report: LIN-MD-31. A phase III, randomized, double-blind, placebo-controlled, parallel-group trial of linaclotide administered orally for 12 weeks followed by a 4-week randomized withdrawal period in patients with irritable bowel syndrome with constipation [**CONFIDENTIAL** internal manufacturer's report]. Jersey City (NJ): Forest Research Institute, Inc.; 2011 May 10.
5. Clinical Study Report: MCP-103-302. A phase 3, randomized, double-blind, placebo-controlled, parallel-group trial of linaclotide administered orally for 26 weeks in patients with irritable bowel syndrome with constipation [**CONFIDENTIAL** internal manufacturer's report]. Cambridge (MA): Ironwood Pharmaceuticals, Inc.; 2011 Jun 24.
6. e-CPS [Internet]. Ottawa: Canadian Pharmacists Association; 2015 [cited 2015 Apr 15]. Available from: https://www.e-therapeutics.ca Subscription required.
7. Rao S, Lembo AJ, Shiff SJ, Lavins BJ, Currie MG, Jia XD, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Am J Gastroenterol. 2012 Nov;107(11):1714-24.
8. Chey WD, Lembo AJ, Lavins BJ, Shiff SJ, Kurtz CB, Currie MG, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Am J Gastroenterol. 2012 Nov;107(11):1702-12.
9. Buono JL, Tourkodimitris S, Sarocco P, Johnston JM, Carson RT. Impact of linaclotide treatment on work productivity and activity impairment in adults with irritable bowel syndrome with constipation: results from 2 randomized, double-blind, placebo-controlled phase 3 trials. Am Health Drug Benefits [Internet]. 2014 Aug [cited 2015 Feb 27];7(5):289-97. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4163780/pdf/ahdb-07-289.pdf
10. Williams VS, Nelson LM, Fehnel SE, MacDougall J, Carson RT, Tourkodimitris S, et al. Psychometric validation of symptom severity measures in irritable bowel syndrome with constipation. Aliment Pharmacol Ther. 2014 Aug;40(3):298-308.
11. Quigley EM, Tack J, Chey WD, Rao SS, Fortea J, Falques M, et al. Randomised clinical trials: linaclotide phase 3 studies in IBS-C - a prespecified further analysis based on European Medicines Agency-specified endpoints. Aliment Pharmacol Ther. 2013 Jan;37(1):49-61.
12. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s). In: Linzess (linaclotide). Company: Forest Laboratories Application no.: 202811. Approval date: 08/30/2012 [Internet]. Rockville (MD): FDA; 2012 Aug 16 [cited 2015 Jan 14]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202811Orig1s000TOC.cfm
13. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s). In: Linzess (linaclotide). Company: Forest Laboratories Application no.: 202811. Approval date: 08/30/2012 [Internet]. Rockville (MD): FDA; 2012 Aug 16 [cited 2015 Jan 14]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202811Orig1s000TOC.cfm

14. Actavis Specialty Pharmaceuticals Co. comments on Constella (linaclotide) clinical and pharmacoeconomic reviews, and CDR reviewer's response [**CONFIDENTIAL** internal report]. Ottawa: CADTH; 2015.

15. Patrick DL, Drossman DA, Frederick IO, DiCesare J, Puder KL. Quality of life in persons with irritable bowel syndrome: development and validation of a new measure. Dig Dis Sci. 1998 Feb;43(2):400-11.

16. Reilly MC, Bracco A, Ricci JF, Santoro J, Stevens T. The validity and accuracy of the Work Productivity and Activity Impairment questionnaire - irritable bowel syndrome version (WPAI:IBS). Aliment Pharmacol Ther. 2004;20(4):459-67.

17. Lacy BE, Lembo AJ, MacDougall JE, Shiff SJ, Kurtz CB, Currie MG, et al. Responders vs clinical response: a critical analysis of data from linaclotide phase 3 clinical trials in IBS-C. Neurogastroenterol Motil [Internet]. 2014 Mar [cited 2015 Feb 27];26(3):326-33. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4282394/pdf/nmo0026-0326.pdf

18. MacDougall JE, Johnston JM, Lavins BJ, Nelson LM, Williams VS, Carson RT, et al. An evaluation of the FDA responder endpoint for IBS-C clinical trials: analysis of data from linaclotide phase 3 clinical trials. Neurogastroenterol Motil. 2013 Jun;25(6):481-6.

19. Camilleri M, Lembo AJ, Lavins BJ, MacDougall JE, Carson RT, Williams VS, et al. Comparison of adequate relief with symptom, global, and responder endpoints in linaclotide phase 3 trials in IBS-C. United European Gastroenterol J [Internet]. 2015 Feb [cited 2015 Feb 27];3(1):53-62. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4315678/pdf/10.1177_2050640614555946.pdf

20. Spiegel B, Bolus R, Harris LA, Lucak S, Naliboff B, Esrailian E, et al. Measuring irritable bowel syndrome patient-reported outcomes with an abdominal pain numeric rating scale. Aliment Pharmacol Ther [Internet]. 2009 Dec 1 [cited 2015 Mar 20];30(11-12):1159-70. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2793273/pdf/nihms146527.pdf

21. Drossman D, Morris CB, Hu Y, Toner BB, Diamant N, Whitehead WE, et al. Characterization of health related quality of life (HRQOL) for patients with functional bowel disorder (FBD) and its response to treatment. Am J Gastroenterol. 2007 Jul;102(7):1442-53.

22. Bushnell DM, Martin NL, Ricci JF, Bracco A. Performance of the EQ-5D in patients with irritable bowel syndrome. Value Health. 2006;9(2):90-7.

23. Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res. 2005 Aug;14(6):1523-32.

24. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Guidance for industry irritable bowel syndrome — clinical evaluation of drugs for treatment [Internet]. Silver Spring (MD): FDA; 2012 May. [cited 2015 Mar 20]. Available from: http://www.fda.gov/downloads/Drugs/Guidances/UCM205269.pdf

25. Shim L, Talley NJ, Boyce P, Tennant C, Jones M, Kellow JE. Stool characteristics and colonic transit in irritable bowel syndrome: evaluation at two time points. Scand J Gastroenterol. 2013 Mar;48(3):295-301.

26. Bushnell DM, Reilly MC, Galani C, Martin ML, Ricci JF, Patrick DL, et al. Validation of electronic data capture of the Irritable Bowel Syndrome - Quality of Life measure, the Work Productivity and Activity Impairment questionnaire for irritable bowel syndrome and the EuroQol. Value Health. 2006;9(2):98-105.

27. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990 Dec;16(3):199-208.

28. Sullivan PW, Lawrence WF, Ghushchyan V. A national catalog of preference-based scores for chronic conditions in the United States. Med Care. 2005 Jul;43(7):736-49.

29. Clinical Study Report: LIN-MD-02. An open-label, long-term safety study of oral linaclotide administered to patients with chronic constipation or irritable bowel syndrome with constipation [**CONFIDENTIAL** internal manufacturer's report]. Jersey City (NJ): Forest Research Institute, Inc.; 2012 Nov 5.

30. Clinical Study Report: MCP-103-305. An open-label, long-term safety study of oral linaclotide administered to patients with chronic constipation or irritable bowel syndrome with constipation [**CONFIDENTIAL** internal manufacturer's report]. Cambridge (MA): Ironwood Pharmaceuticals, Inc.; 2012 Oct 18.