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UK clinical experience up to 52 weeks with linaclotide for irritable bowel syndrome with constipation

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Abstract

Background: Linaclotide, a guanylate cyclase C agonist, has been shown in clinical trials to improve symptoms of irritable bowel syndrome with constipation (IBS-C). Here we report data from a real-world study of linaclotide in the UK.

Methods: This 1-year, multicentre, prospective, observational study in the UK enrolled patients aged 18 years and over initiating linaclotide for IBS-C. The primary assessment was change from baseline in IBS Symptom Severity Scale (IBS-SSS) score at 12 weeks, assessed in patients with paired baseline and 12-week data. Change from baseline in IBS-SSS score at 52 weeks was a secondary assessment. Adverse events were recorded.

Results: In total, 202 patients were enrolled: 185 (91.6%) were female, median age was 44.9 years (range 18.1–77.2) and 84 (41.6%) reported baseline laxative use. Mean (standard deviation) baseline IBS-SSS score was 339 (92), with most patients ($n = 129$; 66.8%) classified as having severe disease (score ⩾300). In patients with paired data, there was a significant mean (95% confidence interval) decrease in IBS-SSS score from baseline to 12 weeks [–77.0 (–96.3, –57.7); $p < 0.001$; $n = 124$] and baseline to 52 weeks [–70.7 (–95.0, –46.5); $p < 0.001$; $n = 76$]. Overall, 174 adverse events were reported in 77 (38.1%) patients, most commonly diarrhoea ($n = 54$; 26.7%), abdominal pain ($n = 21$; 10.4%) and abdominal distension ($n = 13$; 6.4%).

Conclusion: Linaclotide significantly improved IBS-SSS score at 12 and 52 weeks. These results provide insights into outcomes with linaclotide treatment over 1 year in patients with IBS-C in real-world clinical practice.

Keywords: irritable bowel syndrome with constipation, linaclotide, observational study

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Introduction

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder characterised by abdominal pain, bloating and an alteration in bowel habits.[1,2] These criteria have been codified by the Rome Foundation and allow subtyping of IBS based on the predominant stool pattern, with subtypes including IBS with constipation (IBS-C), IBS with diarrhoea (IBS-D), IBS with a mixed stool pattern (IBS-M) and unclassified IBS (IBS-U), when the patient's bowel habits cannot be accurately categorised.[2]

According to the Rome III criteria, approximately 11.5% of the European population is estimated to be affected by IBS; IBS-C represents approximately one third of cases, although estimates vary.[3–5] Prevalence estimates with the Rome IV criteria appear to be lower, suggesting that 7.5% of women and 3.6% of men in the UK are affected.[6] IBS is associated with a substantial reduction in quality of life, greater health care resource use and increased costs.[7] In the UK, patients with IBS-C had significantly greater health care resource use, greater

work productivity impairment and poorer physical and mental health status *versus* matched controls.[7,8]

Patients with IBS-C are often recommended, and make use of, lifestyle modifications or over-the-counter medications, such as fibre, nonprescription laxatives or stool softeners, to manage their symptoms.[9,10] However, these therapies are primarily targeted at relief of a single symptom and are often associated with patient dissatisfaction, potentially resulting in the use of multiple therapies as well as repeated switching of medications.[10,11] Failure of existing treatment options to adequately control the symptoms of IBS-C has been shown to result in increased treatment costs and health care resource use.[12]

Linaclotide is a minimally absorbed, 14-amino-acid peptide guanylate cyclase C agonist approved for the treatment of adults with moderate to severe IBS-C in the European Union,[13,14] based on the results of two large phase III clinical trials demonstrating significant improvements in abdominal pain and bowel symptoms with linaclotide treatment *versus* placebo.[15,16] However, data from the clinical trial setting may not accurately reflect real-world experience in clinical practice.

We therefore aimed to assess the impact of linaclotide treatment in patients with IBS-C in a 1-year, prospective, real-world study in the UK. Here we describe the results of this study at 12 and 52 weeks from initiation of linaclotide treatment.

Methods

Study design

We undertook a 1-year, multicentre, prospective, observational, single-arm study conducted in the gastroenterology and specialist surgical departments of eight secondary or tertiary care centres in the UK, with recruitment occurring from 16 January 2015 to 16 October 2015. There were no changes to patient management for the purposes of any part of this study and patients were not required to attend any visits in addition to their routine care, but were required to complete questionnaires during routine visits. The study observation period was 52 weeks in duration following the initiation of linaclotide for each patient. The use of concomitant treatments for IBS-C during the study was permitted, and patients withdrawing from linaclotide treatment may have been offered other treatment options, which were not recorded as part of the study.

The study received independent NHS Research Ethics Committee (REC) approval from the East of England, Hatfield REC (reference 14-EE-1221), and also received NHS Trust/Health Board Research and Development department approval at each study centre. All participants provided written, informed consent. Data can be obtained by contacting IR-medcom@allergan.com.

Study population

Eligible patients were men and women aged 18 years and over who had been initiated on linaclotide therapy, at a standard dose of 290 μg orally once daily, at a participating research centre as part of their usual care, and who were able and willing to complete questionnaires and consented to their medical records being used for research purposes. The study aimed to achieve a high level of recruitment of patients initiating linaclotide therapy at participating centres.

Study assessments

Efficacy assessments and endpoints. The primary objective of this study was to assess change in IBS Symptom Severity Scale (IBS-SSS) score from baseline to 12 weeks after linaclotide treatment initiation. Secondary objectives included change in IBS-SSS score from baseline to 52 weeks after linaclotide initiation, the proportion of patients responding to linaclotide treatment and change in quality of life, assessed with the IBS Quality of Life measure (IBS-QOL) and the EuroQoL, five-item, three-level questionnaire (EQ-5D-3L), from baseline to 12 and 52 weeks.

The IBS-SSS has five domains scored from 0 to 100, with the overall score reported on a scale of 0–500. Higher scores indicate more severe symptoms, and a score reduction of 50 points is considered adequate to reliably indicate improvement.[17] Disease severity is stratified by IBS-SSS score as follows: normal: <75; mild: 75 to <175; moderate: 175 to <300; severe: $\geqslant 300$.[17] The IBS-QOL is a disease-specific measure with an overall score ranging from 0 to 100 and eight subscale scores, with lower scores indicating lower quality of life.

An increase in IBS-QOL score of 14 points is considered to represent a clinically meaningful improvement.[18,19] The EQ-5D-3L is a standardised measure of general health status with two components: the EQ-5D index score, reported on a scale of 0–1, with higher scores indicating better health state, and the EQ visual analogue scale (VAS), reported on a scale of 0–100, with higher scores indicating better health.[20]

Participants were requested to self-complete the validated IBS-SSS questionnaire[17] at baseline (up to a maximum of 3 days following initiation of linaclotide treatment) and at 4 (±1), 12 (±4) and 52 (±4) weeks after treatment initiation with linaclotide, and to complete the validated IBS-QOL[19] and the EQ-5D-3L[21] at baseline and at 12 (±4) and 52 (±4) weeks after linaclotide initiation. At each time point when study questionnaires were completed, participants also completed a questionnaire on laxative use, whether they were still taking linaclotide treatment and, if relevant, the date and reason for linaclotide discontinuation. A patient was recorded as having discontinued linaclotide treatment if they indicated that they were taking linaclotide for fewer than 4 days per week.

Safety assessments. All adverse events (AEs) and adverse drug reactions that occurred during the study period were documented by participating physicians or by enrolled patients *via* patient questionnaires. AEs reported by physicians were assessed for seriousness and severity and whether a causal relationship to linaclotide could not be excluded; patient-reported AEs were not assessed for severity.

Physician-reported AEs were defined as serious if they met any of the following criteria: results in death; is life-threatening; requires inpatient hospitalisation or prolongs existing hospitalisation results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect; is any other medically important event that may jeopardise the patient or may require intervention to prevent one of the other preceding outcomes; or any suspected transmission *via* a medicinal product of an infectious agent.

Statistical analyses

A sample size of approximately 150–200 patients was considered adequate to detect a statistically significant reduction of ⩾50 points in the IBS-SSS score.[17] The primary endpoint was assessed at 12 weeks, and so a sample size of 190–250 participants was planned to account for the possibility of up to 20% of participants discontinuing within the first 12 weeks and not completing the 12-week questionnaire, based on discontinuation rates observed in previous studies.[22]

Data were summarised using descriptive statistics and the significance of within-patient changes from baseline in IBS-SSS score and other quantitative outcomes were assessed using paired *t* tests. A response to linaclotide was defined as a reduction in overall IBS-SSS score of ⩾50, or a reduction in score to less than 150 for patients with a baseline score of ⩾150.[23] Data from patients without paired questionnaires at both baseline and a given time point (4 weeks, 12 weeks or 52 weeks) were excluded from the analysis. Data were analysed using Microsoft Excel 2010© and Stata 14.2®.

Results

Baseline patient demographics and clinical characteristics

Overall, the study invited 230 patients with IBS-C to participate across eight centres. Of these invited patients, 202 consented to participate, with 151 (74.7%) patients meeting the Rome III diagnostic criteria for IBS. Of the 202 patients, 41 (20.3%) reported continuing on linaclotide treatment at 52 weeks (Figure 1). A further 87 (43.1%) patients reported discontinuing linaclotide treatment before 52 weeks. The remaining 74 patients did not provide a complete 52-week questionnaire (n = 42), did not return a 52-week questionnaire for analysis (n = 29) or were lost to follow up (n = 3).

Among the 87 patients discontinuing before 52 weeks, the primary reason was AEs in 51 (25.2%) patients, followed by lack of efficacy in 18 (8.9%) patients. Thirty-eight patients had discontinued by 4 weeks, with 33 discontinuing between 4 and 12 weeks, and 16 discontinuing after 12 weeks of treatment.

Of the 202 patients enrolled, 124 had paired IBS-SSS data for the completed questionnaires at both baseline and 12 weeks, with 76 having baseline

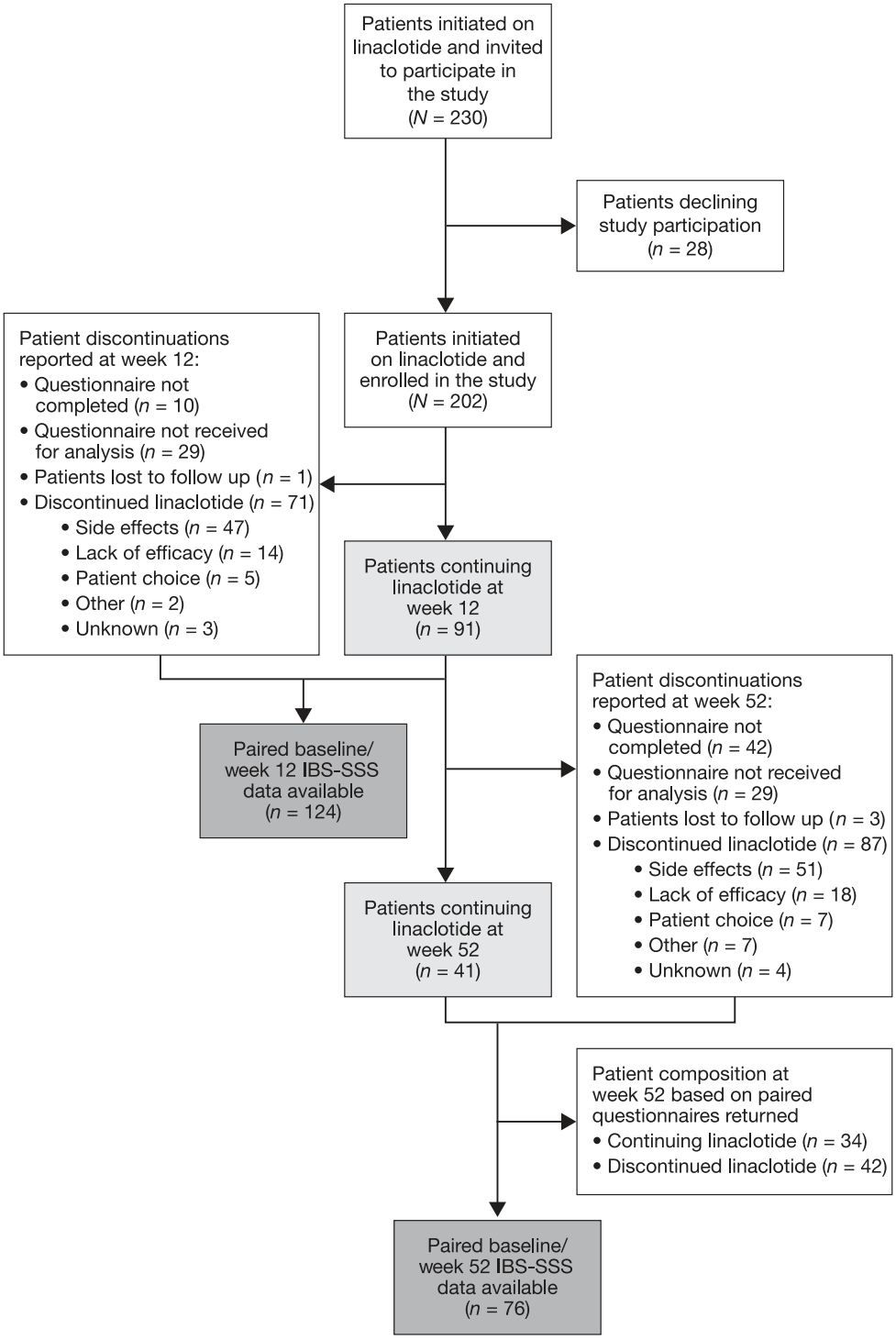

Figure 1. Participant flow.
IBS-SSS, Irritable Bowel Syndrome Symptom Severity Scale.

and 52-week paired IBS-SSS data (Figure 1). Of the 76 patients with paired data at 52 weeks, 34 continued on linaclotide treatment and 42 reported they had discontinued linaclotide treatment.

The median (range) age at baseline was 44.9 (18.1–77.2) years, and the majority of participants (n = 185; 91.6%) were female (Table 1). The median time since diagnosis was 0.21 years.

Table 1. Baseline demographics and clinical characteristics.

	Total (*N* = 202)
Female, *n* (%)	185 (91.6)
Median age (range), years	44.9 (18.1–77.2)
Median time since diagnosis of IBS-C (range), years	0.21 (0–67.7)
Abdominal symptoms, *n* (%)[a]	
Constipation	198 (98.0)
Abdominal pain	169 (83.7)
Bloating	167 (82.7)
Diarrhoea	27 (13.4)
Comorbidities (occurring in ⩾4% of patients), *n* (%)[a]	
Gastroenterology and hepatology	35 (17.3)
Obstetrics and gynaecology	12 (5.9)
Cardiovascular	9 (4.5)
Medications for IBS taken in the 12 months prior to linaclotide initiation (reported by ⩾5% of patients), *n* (%)[a]	
Laxatives	158 (78.2)
Antispasmodics	34 (16.8)
Tricyclic antidepressants	24 (11.9)
Medications for IBS continued at linaclotide initiation (reported by ⩾5% of patients), *n* (%)[a]	
Laxatives	84 (41.6)
Antispasmodics	16 (7.9)
Tricyclic antidepressants	12 (5.9)
Mean IBS-SSS score (SD)[b]	339 (92)
IBS severity based on IBS-SSS score at baseline, *n* (%)[b]	
In remission (IBS-SSS score <75)	1 (0.5)
Mild (IBS-SSS score 75 to <175)	9 (4.7)
Moderate (IBS-SSS score 175 to <300)	54 (28.0)
Severe (IBS-SSS score ⩾300)	129 (66.8)

[a]Not mutually exclusive.
[b]Data available in 193 patients.
IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; IBS-SSS, Irritable Bowel Syndrome Symptom Severity Scale; SD, standard deviation.

The mean (standard deviation) IBS-SSS score at baseline was 339 (92), and the majority of patients (n = 129; 66.8%) had severe IBS-C, based on a baseline IBS-SSS score of ⩾300. The most common medication being taken for IBS at the time of linaclotide treatment initiation and continued during the treatment period was laxatives, reported by 84 (41.6%) patients. Antispasmodics and tricyclic antidepressants were continued at linaclotide initiation by 7.9% and 5.9% of patients, respectively.

Effect of linaclotide treatment on IBS-SSS score

Change from baseline in IBS-SSS score at week 12 and week 52. Among the 124 patients with paired baseline and week 12 data, including those who had discontinued linaclotide prior to week 12 and those still continuing on treatment, the mean IBS-SSS score was significantly reduced from baseline to 12 weeks after linaclotide initiation, with a mean [95% confidence interval (CI)] change of −77.0 (−96.3, −57.7; $p < 0.001$) [Figure 2(a)]. A similar reduction was seen among patients with paired data at week 52: mean IBS-SSS score was significantly reduced from baseline to 52 weeks, with a mean (95% CI) change of −70.7 (−95.0, −46.5; $p < 0.001$) [Figure 2(b)].

Of the patients with paired IBS-SSS data at week 12, 91 had a reduced IBS-SSS score at week 12

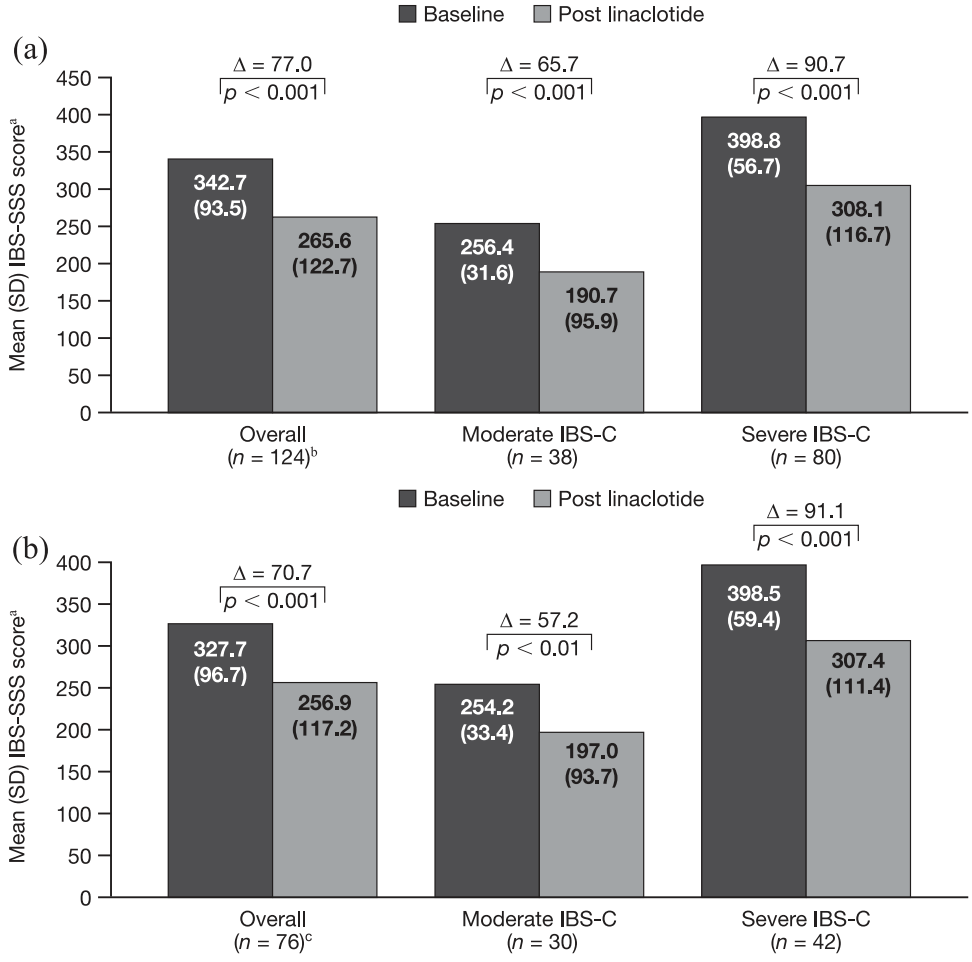

Figure 2. Change in IBS-SSS score in the overall population and by baseline severity at 12 weeks (a) and 52 weeks (b).

[a]Scored from 0 to 500; [b]includes six patients with IBS-C classified as mild at baseline; [c]includes four patients with IBS-C classified as mild at baseline.

IBS-C, irritable bowel syndrome with constipation; IBS-SSS, Irritable Bowel Syndrome Symptom Severity Scale; SD, standard deviation.

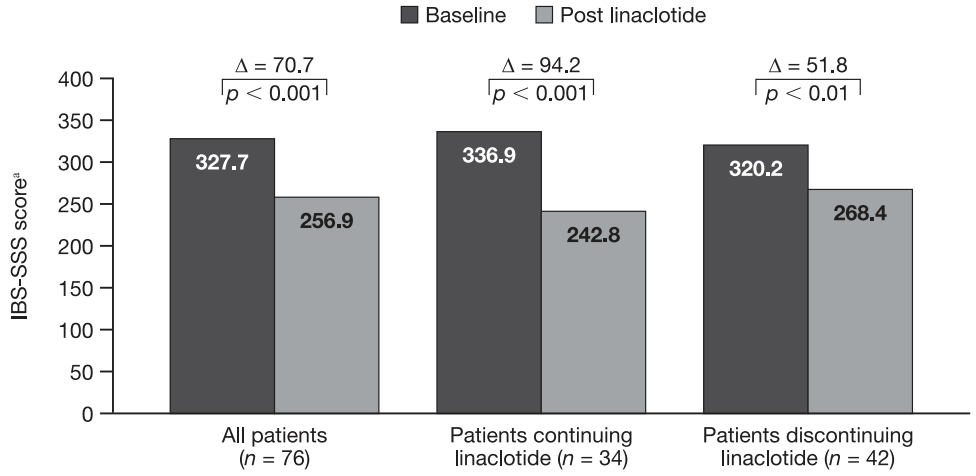

Figure 3. Change in IBS-SSS score at 52 weeks in patients continuing or discontinuing linaclotide.
[a]Scored from 0 to 500.
IBS-SSS, Irritable Bowel Syndrome Symptom Severity Scale.

versus baseline, with 66 meeting the threshold of a reduction of ⩾50 points. Four patients had no change in score, and 29 had an increased score, indicating worsening symptoms. Of the 76 patients with paired IBS-SSS data at week 52, 55 experienced a decrease in IBS-SSS score *versus* baseline, with 40 experiencing a decrease of ⩾50 points. One patient had no change in score and 20 patients had an increase in score.

At week 12, a greater mean (95% CI) change from baseline in IBS-SSS score was observed in patients with severe IBS-C [−90.7 (−115.8, −65.7); $p < 0.001$] compared with patients with moderate IBS-C [−65.7 (−96.4, −35.0); $p < 0.001$] and the overall population [Figure 2(a)]. Similar results were seen at week 52, with a greater mean (95% CI) change in patients with severe IBS-C [−91.1 (−125.8, −56.5); $p < 0.001$] *versus* patients with moderate IBS-C [−57.2 (−90.7, −23.8); $p < 0.01$] and the overall population [Figure 2(b)].

When patients with paired 52-week data were stratified according to whether they continued on linaclotide treatment or had discontinued before 52 weeks, the mean (95% CI) change in IBS-SSS score from baseline to week 52 was significant both in patients continuing on linaclotide treatment [−94.2 (−129.8, −58.5); $p < 0.001$] and in patients who had discontinued linaclotide [−51.8 (−85.1, −18.5); $p < 0.01$] (Figure 3).

Response to linaclotide treatment. At 12 and 52 weeks, 55.6% and 53.9% of patients, respectively, with paired data displayed a response to linaclotide treatment (Figure 4). The proportion of responders at week 12 and week 52 was broadly similar to the overall population, both in patients reporting moderate IBS-C symptoms at baseline (57.9% and 46.7%, respectively) and in patients reporting severe symptoms at baseline (55.0% and 59.5%, respectively).

Effect of linaclotide treatment on quality of life

Changes in IBS-QOL score at 12 and 52 weeks. Linaclotide treatment significantly improved IBS-QOL total scores, with a mean (95% CI) change from baseline of 8.7 (5.8, 11.6) points ($p < 0.001$) at 12 weeks and 12.2 (8.3, 16.0) points ($p < 0.001$) at 52 weeks [Figure 5(a)]. A significant improvement of approximately 10–15 points *versus* baseline was seen at both 12 and 52 weeks after linaclotide treatment initiation across all subscales of the IBS-QOL ($p < 0.05$ for all comparisons) [Figure 5(b)]. The greatest mean (95% CI) changes at week 52 were seen for the health worry and dysphoria subscales, with improvements of 15.1 (10.0, 20.3) and 12.8 (8.3, 17.3) points, respectively.

Changes in EQ-5D-3L at 12 and 52 weeks. Mean EQ-5D index overall scores were significantly increased from baseline to week 12, with a mean (95% CI) change of 0.09 (0.05, 0.13) points ($p < 0.001$), but were similar from baseline to week 52, with a mean (95% CI) change of −0.005 (−0.05, 0.06; $p > 0.1$) [Figure 6(a)].

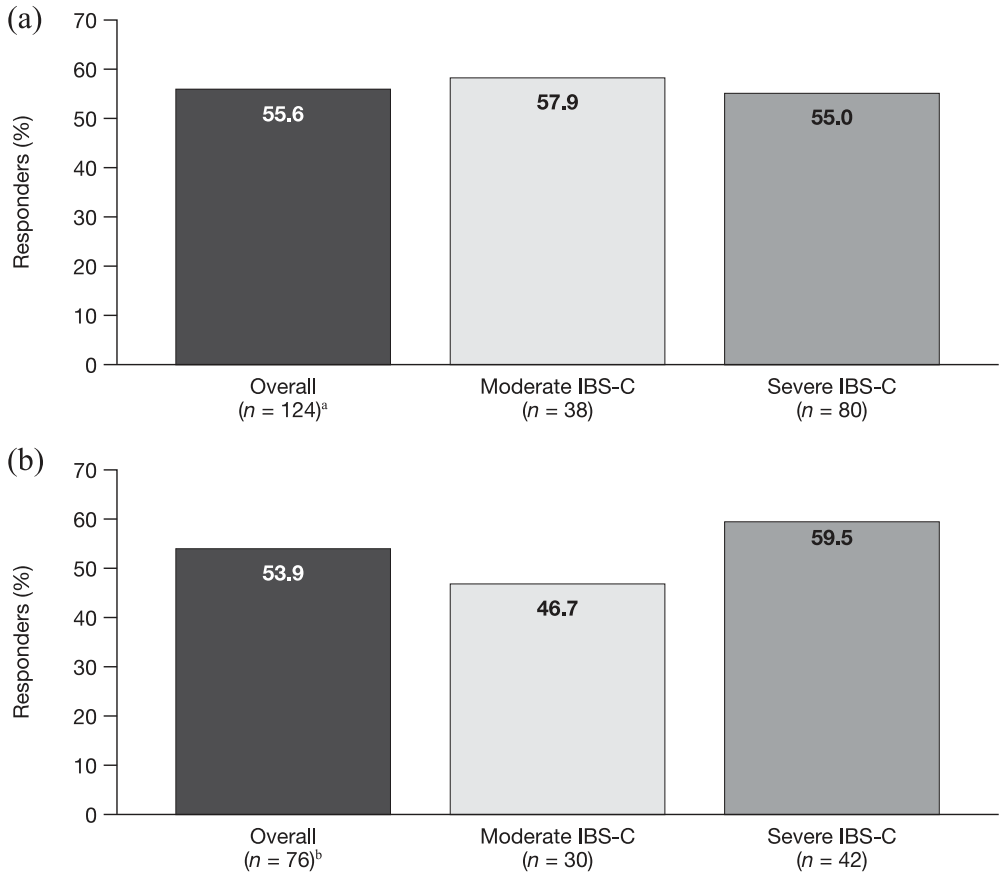

Figure 4. Response to linaclotide in the overall population and by baseline severity at 12 weeks (a) and 52 weeks (b). Response to linaclotide was defined as a reduction in IBS-SSS overall score of ⩾50, or a reduction in score to <150 for patients with a baseline score of ⩾150.
[a]Includes six patients with IBS-C classified as mild at baseline; [b]includes four patients with IBS-C classified as mild at baseline.
IBS-C, irritable bowel syndrome with constipation; IBS-SSS, Irritable Bowel Syndrome Symptom Severity Scale.

EQ-VAS overall scores were also significantly improved following linaclotide treatment initiation, with a mean (95% CI) change from baseline of 7.9 (4.0, 11.8) points ($p < 0.001$) at week 12 and 6.1 (0.03, 12.2) points ($p < 0.05$) at week 52 [Figure 6(b)].

Safety

Overall, 77 (38.1%) patients reported 174 AEs during the 52-week study (Table 2). The most commonly reported AEs were diarrhoea (26.7%), abdominal pain (10.4%) and abdominal distention (6.4%). By week 12, 47 (23%) patients had discontinued the study due to AEs, and by 52 weeks, this number had increased to 51 patients (26%).

Of the AEs reported, 73 (42.0%) were assessed as not serious, 8 (4.6%) were serious and the remainder (93; 53.4%) had no assessment of seriousness recorded. The eight serious AEs were as follows: two events of spontaneous abortion occurring in one patient (1.1%; relationship to study drug unknown); one event of diarrhoea occurring in each of two patients (1.1%; both considered drug related); and one event in one patient each of abdominal discomfort (considered drug related), abdominal pain (considered drug related), constipation (relationship to study drug unknown) and rectal bleeding (considered probably drug related) [0.6% each].

A *post hoc* analysis demonstrated that 42 (50%) patients with baseline laxative use reported at least one AE during the study period, compared with 35 (30%) among patients not reporting baseline laxative use. AEs of diarrhoea were also more common in patients with baseline laxative use (32%) *versus* patients without baseline laxative use (20%). However, a χ^2 test showed that

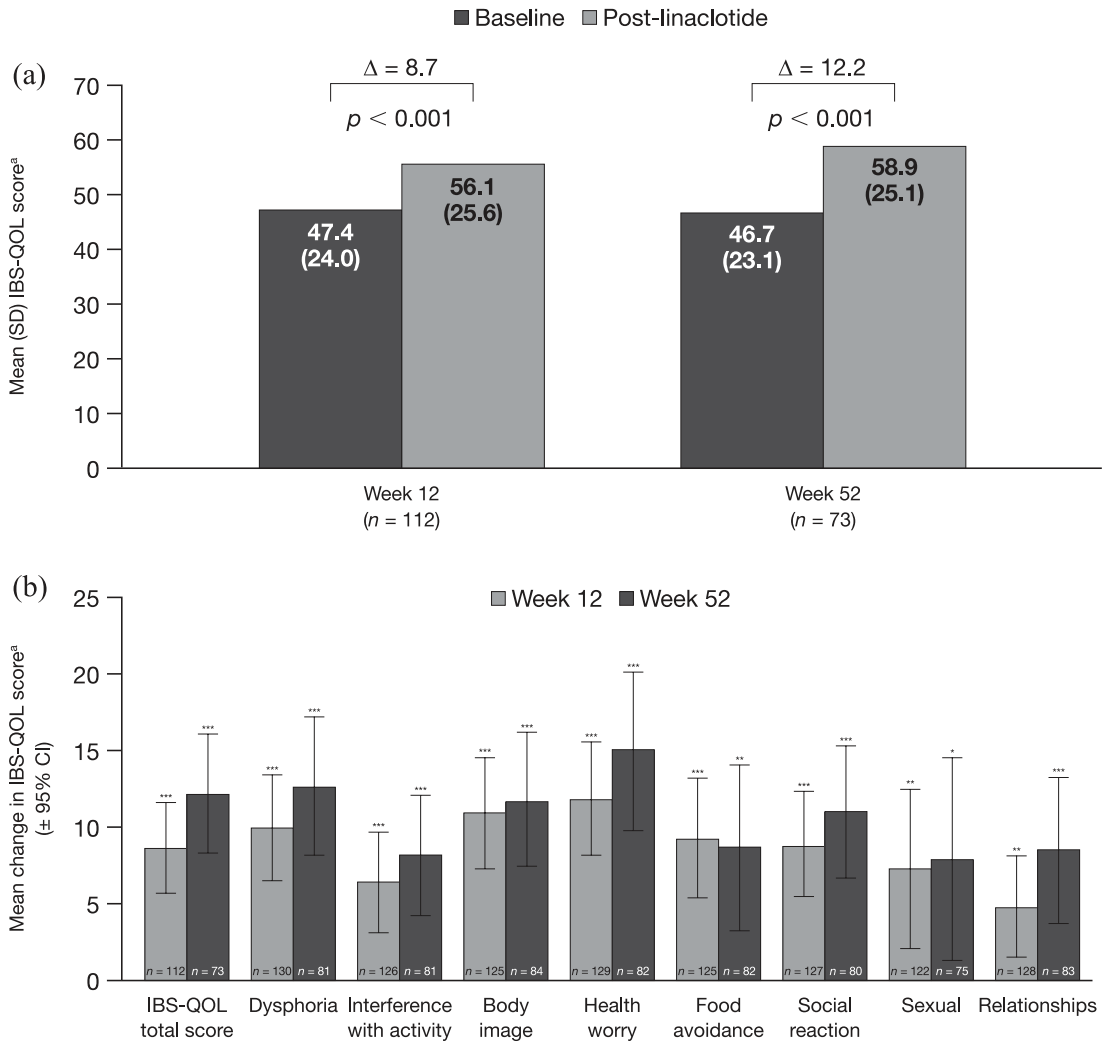

Figure 5. IBS-QOL overall score at 12 and 52 weeks (a) and change from baseline in IBS-QOL overall score and domain scores at 12 and 52 weeks (b).
[a]Scored from 0 to 100 (higher scores indicate better functioning).
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
CI, confidence interval; IBS-QOL, Irritable Bowel Syndrome Quality of Life; SD, standard deviation.

the association between baseline laxative use and experiencing AEs of diarrhoea within 12 weeks of treatment initiation was not significant (odds ratio: 1.86; $p = 0.057$).

Discussion

The efficacy and safety of linaclotide were assessed in patients with moderate to severe IBS-C in the real-world setting in this 1-year, prospective, observational, open-label study conducted in gastroenterology and specialist surgical departments of secondary and tertiary care centres in the UK. Baseline patient characteristics, including severity scores and prior medication use, suggest that the patient cohort in this study experienced IBS-C symptoms towards the more severe end of the spectrum and may have been refractory to prior treatment. Symptom severity assessed with the IBS-SSS was significantly reduced compared with baseline at 12 and 52 weeks of linaclotide treatment among patients with paired data. These reductions were observed in patients with moderate IBS-C and with severe IBS-C, with a slightly greater change from baseline to week 12 and week 52 seen in patients with severe IBS-C *versus* the moderate subgroup and the overall population. Patients withdrawing from linaclotide therapy were offered other therapy options, although these were not recorded as

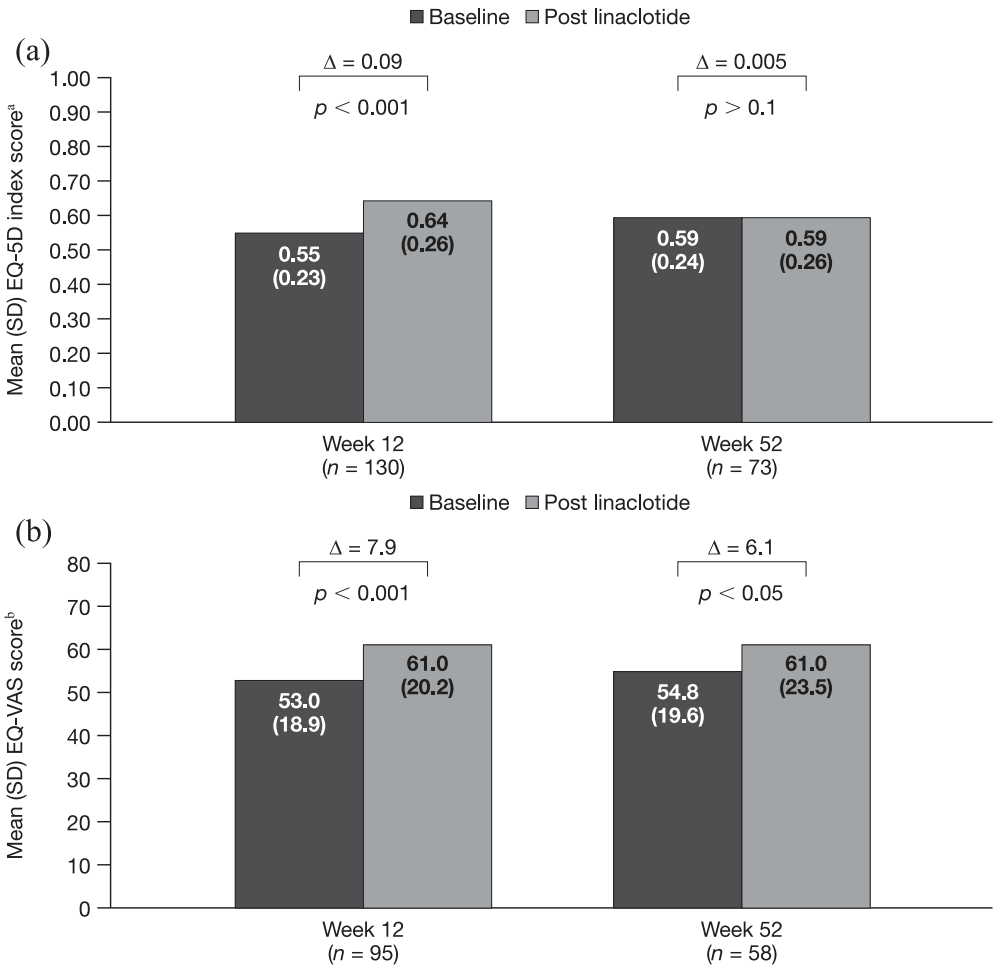

Figure 6. EQ-5D index overall score at 12 and 52 weeks (a) and EQ-VAS score at 12 and 52 weeks (b).
[a]Scored from 0 to 1 (1 indicates full health); [b]scored from 0 to 100 (higher scores indicate better health state).
EQ-5D, EuroQol five dimension; EQ-VAS, EuroQol visual analogue scale; SD, standard deviation.

part of the study, which may have been responsible for the reduction in severity at 52 weeks in the overall population, observed irrespective of whether patients had reported that they discontinued linaclotide treatment prior to 52 weeks or continued on treatment.

Current guidance from the UK National Institute for Health and Care Excellence for the diagnosis and management of IBS states that linaclotide should be considered if optimal or maximal tolerated doses of previous laxatives from different classes have not helped and the patient has had constipation for at least 12 months.[24] In line with these guidelines, nearly 80% of patients in this study had used laxatives within the 12 months prior to linaclotide initiation, with approximately 40% still taking laxatives at the time of linaclotide initiation. As treatment failure in patients with IBS-C is known to result in increased health care resource use and costs,[12] the finding from this study that linaclotide treatment is able to significantly reduce symptom severity is important.

The present data support the previously reported findings of two large phase III clinical trials of linaclotide in over 1500 patients with moderate to severe IBS-C, which demonstrated significant reductions in IBS severity with linaclotide treatment *versus* placebo.[15,16] These data are also in line with the results from an observational study of linaclotide conducted in clinical practice in Germany ($N = 375$), where linaclotide treatment led to significant reductions in intensity of abdominal pain and bloating and improved bowel movement frequency *versus* baseline.[25]

The threshold for improvement in IBS-SSS overall score in this study was a reduction of ⩾50 points, in line with numerous studies making use of the

Table 2. Summary of AEs, regardless of relationship to study drug.

	Total (*N* = 202)
Total number of AEs	174
Patients with ⩾1 AE, *n* (%)[a]	77 (38.1)
Not serious[b]	73 (42.0)
Serious[b]	8 (4.6)
No assessment of seriousness recorded[b]	93 (53.4)
AEs occurring in ⩾1.5% of patients, *n* (%)[c]	
Diarrhoea[d]	54 (26.7)
Abdominal pain	21 (10.4)
Abdominal distension	13 (6.4)
Anal incontinence	8 (4.0)
Nausea	8 (4.0)
Defecation urgency	5 (2.5)
Dyspepsia	5 (2.5)
Headache	5 (2.5)
Vomiting	4 (2.0)
Condition aggravated	3 (1.5)
Constipation	3 (1.5)
Gastrointestinal sounds abnormal	3 (1.5)
Malaise	3 (1.5)
Muscle spasms	3 (1.5)

[a]Includes AEs where the relationship to study drug is related, probable, possible or unknown.
[b]Expressed as a proportion of 174 events reported.
[c]Expressed as number of events (percentage of patients).
[d]Includes events of loose stools coded as diarrhoea.
AE, adverse event.

IBS-SSS and the original description of this measure.[17,26–30] However, a single study based on a cohort of 277 patients with IBS has suggested that a change of 95 points might represent a minimal clinically important difference.[31] A 50% improvement from baseline in IBS-SSS score has also been proposed as a responder definition; however, this criterion requires further validation.[32–34]

Linaclotide treatment also led to significant improvements in quality of life. Pooled analysis of the linaclotide phase III trials demonstrated that linaclotide led to significant improvements *versus* placebo in quality of life, as assessed with the IBS-QOL,[35] with over half of linaclotide-treated patients displaying a response after 12 weeks of treatment. These findings are supported by the significant improvements seen in IBS-QOL total score and across all subscales in the present study at both 12 and 52 weeks.

The most common AEs reported with linaclotide treatment in the present study were diarrhoea and abdominal pain. The safety profile observed with

linaclotide in this 1-year study is similar to that seen in the phase III trials, with no signs of additional adverse events developing as a result of prolonged use.[15,16] AEs of diarrhoea that were related, probably or possibly related, or unrelated to the study drug were reported in 26.7% of patients in the present study, and were reported (regardless of relatedness) in 19.5% and 19.7% of patients in the two phase III studies, respectively.[15,16] The higher incidence of diarrhoea observed in this study may be attributable to approximately 40% of patients continuing laxative use after linaclotide initiation. In the present study, AEs of diarrhoea were more common among patients with baseline laxative use *versus* patients without. These findings are in line with the recommendation that linaclotide should not be coadministered with laxatives at the start of treatment.[14]

At 52 weeks, a high proportion of patients had discontinued treatment with linaclotide. The majority of patients discontinuing linaclotide treatment did so within the first 4 weeks, with only a small proportion of patients who continued on linaclotide after 12 weeks subsequently discontinuing. The most common reason for discontinuation was AEs, occurring in 25.2% of patients. In the two phase III studies, 7.9% and 10.2% of patients in the linaclotide treatment group discontinued due to a treatment-emergent AE.[15,16] The higher rate of discontinuations due to AEs reported in the present study may be attributable to the manner in which the data were collected. Patients indicated whether they had taken linaclotide for fewer than 4 days over the past week; if they answered 'yes', they were considered to have discontinued. However, this could have been a temporary interruption of treatment and not a permanent discontinuation. Furthermore, this was a low-intensity, observational study with limited face-to-face study visits, and higher discontinuation rates may therefore be expected compared to those seen in a phase III study with more intensive patient follow up and more frequent patient contact. These results may therefore represent a more 'real-world' outcome.

The findings of this study should also be interpreted in the light of other limitations. First, the study was observational in nature and did not have a comparator group. The study also enrolled a number of patients who did not meet Rome III criteria and a small number of patients with IBS that was mild or in remission at baseline; such patients would typically be excluded from a phase III trial, but are reflective of the population with IBS seen in clinical practice. Second, the findings may have been influenced by confounding factors, such as changes in concomitant medications, including laxatives, or initiation of alternative medications after linaclotide discontinuation, which were not recorded during the study. For instance, patients were not required to cease laxative use at baseline, and the types of laxatives used were not collected from the trial population. Furthermore, patients discontinuing linaclotide treatment and initiating an alternative treatment option may have continued to return study questionnaires after stopping linaclotide. Third, completed patient questionnaires were not available for every patient at every time point, meaning that analyses are based only on data from those patients who had paired questionnaires. Finally, the study sample size was calculated to ensure sufficient power for the primary analysis. However, due to patient discontinuations and paired data not being available for every patient, other statistical analyses may not have been appropriately powered and should be considered descriptive only.

Overall, the results of this 1-year, prospective, observational, open-label study represent the first report of a 1-year, real-world study of linaclotide in the UK, and demonstrate that linaclotide treatment is effective in improving the severity of IBS-C with a favourable and consistent safety profile. There was a high rate of discontinuations in this study, partly related to the prevalence of AEs of diarrhoea, with patients not showing a response typically discontinuing early, and those continuing on treatment maintaining a response. These data support the findings of the linaclotide phase III clinical trials and show that the findings translate into the real-world setting of secondary and tertiary care centres in the UK.

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