Linaclotide: new mechanisms and new promise for treatment in constipation and irritable bowel syndrome

Ther Adv Chronic Dis

(2013) 4(6) 268–276

DOI: 10.1177/2040622313500110

Ruchit Sood and Alexander C. Ford

Abstract: Chronic idiopathic constipation (CIC) and irritable bowel syndrome (IBS) are functional disorders of the lower gastrointestinal tract. Their prevalence in the general population is between 5% and 20%. Both disorders are chronic, with a relapsing and remitting natural history. The medical treatment of both conditions is unsatisfactory at present, and they represent a huge burden to the health service. Linaclotide is a first-in-class minimally adsorbed, 14-amino-acid peptide agonist of guanylate cyclase C. The drug acts on the intestinal enterocyte. As a consequence of this, intestinal fluid secretion is increased and intestinal transit is accelerated. The efficacy of linaclotide has been studied in both CIC and constipation-predominant IBS (IBS-C). Randomized controlled trials consistently demonstrate that the drug is effective in the treatment of CIC and IBS-C, across a wide range of continuous and dichotomous endpoints. The number needed to treat with linaclotide to prevent one patient with CIC or IBS-C failing to respond to therapy is between 5 and 8 in studies that have reported these data. Overall, in the majority of trials, total numbers of adverse events have been no more frequent with linaclotide, but rates of diarrhoea have been consistently higher. While the drug is clearly effective in the treatment of CIC, there are other evidence-based therapies available, and head-to-head efficacy and cost-effectiveness studies are therefore required to further delineate the role of linaclotide in the treatment of the condition. In IBS-C there are no other licensed therapies available, and linaclotide therefore represents a novel treatment with great promise.

Keywords: abdominal pain, constipation, diarrhoea, irritable bowel syndrome, linaclotide

Introduction

Irritable bowel syndrome (IBS) and chronic idiopathic constipation (CIC) are functional disorders of the lower gastrointestinal (GI) tract. The gold standard for the diagnosis of both conditions is the ROME criteria. IBS is characterized by the presence of abdominal pain or discomfort in association with altered stool form or frequency [Longstreth *et al.* 2006], while criteria for CIC include persistently difficult, infrequent, or incomplete defecation, in the absence of any physiological abnormality [Longstreth *et al.* 2006]. The prevalence of IBS and CIC varies between 5% and 20% depending on the criteria used to define them [Lovell and Ford, 2012c; Suares and Ford, 2011b].

IBS and CIC are more common in women [Lovell and Ford, 2012b; Suares and Ford, 2011b] and IBS is more common in younger individuals [Lovell and Ford, 2012c], while the prevalence of CIC appears to increase with age [Suares and Ford, 2011b]. The two disorders follow a relapsing and remitting course. There is no evidence that IBS is associated with a reduced life expectancy [Ford *et al.* 2012] but CIC has been associated with a slight increase in mortality in the community [Chang *et al.* 2010], although the reasons for this are unclear. Despite their functional nature, both conditions are associated with significant impairments in quality of life [Drossman *et al.* 2000; Wald *et al.* 2007] of a similar magnitude to that experienced by patients with chronic organic

Correspondence to:
Alexander C. Ford, MBChB, MD, FRCP
Leeds Gastroenterology Institute, St James's University Hospital, Room 125, 4th Floor, Bexley Wing, Beckett Street, Leeds LS9 7TF, UK
alexf12399@yahoo.com

Ruchit Sood, MBChB, MRCP
Leeds Gastroenterology Institute, St James's University Hospital, Leeds, UK

disorders. The financial burden of IBS and CIC to society is considerable due to direct costs to the healthcare system, such as consultations, investigations and drug therapy [Maxion-Bergemann *et al.* 2006; Peery *et al.* 2012] and indirect costs arising from lost days at work and absenteeism.

Effective therapies exist for both conditions [Ford *et al.* 2008, 2009a, 2009b; Ford and Suares, 2011; Moayyedi *et al.* 2010; Suares and Ford, 2011a] but none are proven to alter the long-term natural history. As a result, treatment tends to be targeted towards the predominant symptom experienced in IBS, while in CIC the aim is to improve stool consistency and frequency. Despite attempts to classify the functional GI disorders separately, there appears to be a large degree of overlap between them [Ford *et al.* 2010; Lovell and Ford, 2012a; Suares and Ford, 2011b]. A recent study demonstrated a lack of stability in the diagnosis of both constipation-predominant IBS (IBS-C) and CIC during follow up [Wong *et al.* 2010], suggesting that the two are not entirely separate conditions. This underlines the potential for new therapies to be developed which are effective in the management of both IBS-C and CIC.

What is linaclotide?

Linaclotide is a first-in-class minimally adsorbed, 14-amino-acid peptide agonist of guanylate cyclase C (GC-C). It binds to, and activates, GC-C receptors on the luminal surface of the intestinal enterocyte. This increases the production of cyclic guanosine monophosphate, which in turn triggers a signal transduction cascade that leads to activation of the cystic fibrosis transmembrane conduction regulator, resulting in the release of chloride and bicarbonate into the intestinal lumen. As a consequence, intestinal fluid secretion is increased and intestinal transit is accelerated [Busby *et al.* 2010]. This mechanism of action explains its therapeutic potential in CIC. In addition, linaclotide appears to have beneficial effects in rodent models of visceral pain [Eutamene *et al.* 2010] that are also mediated via GC-C, including antinociceptive properties. This led to the hypothesis that it may also be efficacious in IBS-C, and hence the more recent studies conducted in this condition. Randomized, controlled trials of linaclotide in both CIC and IBS-C are summarized below, and details of individual studies are provided in Table 1.

What is the evidence supporting linaclotide in chronic idiopathic constipation?

Phase IIa study

In a randomized, double-blind, placebo-controlled phase IIa pilot study to evaluate the effects of linaclotide in CIC, 42 patients were randomized to linaclotide (100, 300 or 1000 μg) or placebo once daily for 2 weeks [Johnston *et al.* 2009]. The mean age of patients was 45 years and 88% were women. Eligible individuals had to report less than three spontaneous bowel movements (SBMs) per week, along with one or more of lumpy or hard stools, straining and a sense of incomplete evacuation on at least 25% of bowel movements.

After 2 weeks of therapy there were numerically greater increases in SBMs, complete spontaneous bowel movements (CSBMs), and also improvements in stool consistency and straining, measured by the ease of passage score. CSBM frequency, stool consistency and straining scores improved in a dose-dependent manner. Improvements were also demonstrated in abdominal discomfort, severity of constipation and overall symptom relief. Compared with placebo, linaclotide 100 μg significantly increased the frequency of SBMs (p = 0.047), and linaclotide 1000 μg significantly improved stool consistency (p = 0.014). No dichotomous data concerning response to therapy were reported in this phase IIa study. The commonest adverse events with active therapy reported in this study were diarrhoea and abdominal pain, but all of these were judged as mild or moderate in severity by the investigators.

Phase IIb study

Following the previous study, a phase IIb multicentre, randomized, double-blind, placebo-controlled trial was conducted in 310 patients with CIC [Lembo *et al.* 2010]. The study was conducted at 57 clinical centres in the USA. The mean age of patients was 47 years and 92% were women. Eligibility criteria were similar to those for the phase IIa trial, and patients were randomized in approximately equal numbers to receive 75, 150, 300 or 600 μg of linaclotide, or placebo, once daily for 4 weeks. The primary endpoint was the change in mean weekly SBM frequency from baseline during the 4-week treatment period. Other endpoints included CSBM frequency, stool consistency, straining, SBM response rates (defined as at least three SBMs per week with an

Table 1. Characteristics of randomized, placebo-controlled trials in chronic idiopathic constipation (CIC) and constipation-predominant irritable bowel syndrome (IBS-C).

Study	Phase	Condition	Number of patients (% women)	Dose of linaclotide studied (μg)	Endpoints met
Johnson *et al.* [2009]	IIa	CIC	42 (88)	100, 300, 1000	SBM frequency Stool consistency
Lembo *et al.* [2010]	IIb	CIC	310 (92)	75, 150, 300, 600	SBM frequency SBM within first 24 h SBM responder rates CSBM responder rates Stool consistency Straining Abdominal discomfort Bloating Treatment satisfaction Quality of life
Lembo *et al.* [2011] (trial 303)	III	CIC	642 (87)	145, 290	CSBM responder CSBM and SBM frequency Stool consistency Straining Abdominal discomfort Bloating Treatment satisfaction Quality of life
Lembo *et al.* [2011] (trial 01)	III	CIC	630 (90.5)	145, 290	CSBM responder CSBM and SBM frequency Stool consistency Straining Abdominal discomfort Bloating Treatment satisfaction Quality of life
Andresen *et al.* [2007]	IIa	IBS-C	36 (100)	100, 1000	Ascending colon emptying time Time to first bowel movement Stool frequency Stool consistency Ease of stool passage
Johnston *et al.* [2010]	IIb	IBS-C	420 (92)	75, 150, 300, 600	CSBM and SBM frequency CSBM responder SBM responder Adequate relief responder Global relief responder Stool consistency Straining Abdominal pain Abdominal discomfort Bloating
Chey *et al.* [2012]	III	IBS-C	804 (90)	290	FDA responder CSBM and SBM frequency Abdominal pain, discomfort, bloating, fullness, and cramping Stool consistency Straining Adequate relief Treatment satisfaction

(Continued)

Table 1. (Continued)

Study	Phase	Condition	Number of patients (% women)	Dose of linaclotide studied (μg)	Endpoints met
Rao *et al.* [2012]	III	IBS-C	800 (90.5)	290	FDA responder CSBM and SBM frequency Abdominal pain, discomfort, bloating, fullness, and cramping Stool consistency Straining Adequate relief Treatment satisfaction

CSBM, complete spontaneous bowel movement; FDA, US Food and Drug Administration; SBM, spontaneous bowel movement.

increase of at least one from baseline for 3 out of 4 weeks of therapy), CSBM response rates (defined similarly to SBM response rates), treatment satisfaction and effect on quality of life [using the Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaire].

There was a dose-dependent increase in weekly SBM frequency (2.6, 3.3, 3.6 and 4.3 for 75, 150, 300 and 600 μg of linaclotide respectively, linear-trend $p < 0.001$), compared with 1.5 for placebo. The mean number of CSBMs per week was also increased in a dose-dependent manner. Stool consistency and straining improved significantly and with a dose–response effect. SBM responder rates ranged between 55% and 68% with linaclotide compared with 32% for placebo ($p \leq 0.01$ for all doses), and CSBM responder rates from 19% to 32% compared with 7% for placebo ($p \leq 0.05$ for all doses except 75 μg). Following cessation of therapy, bowel habits returned towards baseline levels. Patient satisfaction with therapy was significantly greater in all four of the linaclotide arms, and quality-of-life scores were significantly higher with 75, 150 and 600 μg of linaclotide. Total numbers of adverse events were similar with linaclotide and placebo, although the number of patients reporting diarrhoea with active therapy was numerically higher.

Phase III studies

The results of two phase III, multicentre, randomized, double-blind, placebo-controlled trials involving 1276 patients with CIC (trial 303 and trial 01) were published in 2011 [Lembo *et al.* 2011]. The studies were conducted in the USA and Canada. The mean age of patients in each arm of the two trials ranged from 47 to 49 years and 87–90.5% were women. Eligibility criteria were identical to those for the phase IIb trial. Patients who met the inclusion criteria were entered into a 12-week treatment period and randomized to receive linaclotide 145 or 190 μg, or placebo. The adjustment in total dose of the drug from the phase IIa and IIb studies does not reflect a change in the amount of linaclotide used in these clinical trials, but resulted from improved methods used to measure linaclotide content.

After completing the 12 weeks of treatment, subjects in trial 303 were then entered into a 4-week, double-blind period of randomized withdrawal. Patients who had received linaclotide in the previous 12 weeks were randomized to receive either the dose of linaclotide that they had received previously or placebo, and those who had received placebo previously were assigned to linaclotide 290 μg. The primary endpoint of the trials was achieving at least three CSBMs per week, with an increase of at least one CSBM per week from baseline for 9 or more weeks during the 12-week treatment period. Secondary endpoints included the effect of linaclotide on stool frequency, stool consistency, straining, satisfaction with treatment, and health-related quality of life, again using the PAC-QOL questionnaire.

In trials 303 and 01, 21% and 16% who received linaclotide 145 μg and 19% and 21% who received 290 μg met the primary endpoint for response respectively compared with 3% and 6% who received placebo ($p < 0.01$). Differences in the overall response rates between the two linaclotide arms were not significant in either trial. There were significant improvements from baseline to week 12 in all secondary endpoints with linaclotide compared with placebo. Treatment satisfaction scores

were significantly higher with active therapy and the proportion of patients with an improvement in PAC-QOL score of at least 1 from baseline was also significantly higher with linaclotide.

In trial 303 among patients continuing to take linaclotide and those who were rerandomized from placebo to linaclotide, the increase in CSBMs remained similar to those during the initial 12 weeks of therapy, while among those who were rerandomized from linaclotide to placebo, CSBMs returned to a similar level to that of the patients originally assigned to placebo. However, there was no evidence of rebound worsening of symptoms. Serious adverse events were no more common with linaclotide, but again absolute numbers of patients reporting diarrhoea were higher with active therapy.

Systematic review and meta-analysis of randomized controlled trials

In a systematic review and meta-analysis of the three trials that reported dichotomous outcome data [Lembo *et al.* 2010, 2011], 860 of 1089 patients (79%) receiving linaclotide failed to respond to therapy, compared with 468 of 493 (95%) placebo patients [Ford and Suares, 2011]. The relative risk of failure to respond to therapy was significantly lower with linaclotide [0.84; 95% confidence interval (CI) 0.80–0.87], with no significant heterogeneity between studies. The number needed to treat with linaclotide was 6 (95% CI 5–8). Analyses according to the dose of linaclotide used demonstrated similar efficacy for 145 μg and 290 μg. All three trials reported the number of patients experiencing diarrhoea, which was more common with linaclotide (relative risk 3.08; 95% CI 1.27–7.48).

What is the evidence supporting linaclotide in constipation-predominant irritable bowel syndrome?

Phase IIa study

The results of the first phase IIa double-blind placebo-controlled dose-ranging study to investigate the effects of linaclotide in patients with IBS-C were published in 2007 [Andresen *et al.* 2007]. In this trial 36 women who met the ROME II criteria for IBS were randomized in a 1:1:1 ratio to receive linaclotide 100 μg, linaclotide 1000 μg or placebo once daily for 5 days. Trial medication was administered as an oral solution, which was thawed each morning. In order to be enrolled in the study, participants had to demonstrate slow colonic transit at baseline, as measured by scintigraphy. Primary endpoints were the ascending colon emptying half time and overall colonic transit time at 24 h, again measured using scintigraphy. The authors also collected data concerning stool frequency and consistency, ease of stool passage, sense of complete emptying of bowels and time to first bowel movement after drug intake. No dichotomous data concerning response to therapy were reported in this phase IIa study.

Linaclotide led to a significant effect on ascending colon emptying half time but only for the 1000 μg dose compared with placebo ($p = 0.004$). Overall colonic transit time at 48 h was also accelerated significantly with 1000 μg compared with placebo ($p = 0.01$), although the effect at 24 h was not statistically significant. Time to first bowel movement was significantly lower with linaclotide 1000 μg and 100 μg (512 and 487 min respectively *versus* 750 min with placebo, $p = 0.013$), and there were significant increases in stool frequency ($p = 0.037$), improvements in stool consistency ($p < 0.001$) and ease of stool passage ($p < 0.001$) in a dose-dependent manner.

No serious adverse events were reported and no patients discontinued therapy due to adverse events. The most commonly reported adverse events were headache, abdominal bloating, and borborygmi, which were numerically higher among those assigned to active therapy.

Phase IIb study

In 2010 the results of a randomized phase IIb, double-blind, parallel group, placebo-controlled trial were published [Johnston *et al.* 2010]. This was a multicentre study conducted in the United States and Canada, recruiting 420 patients with IBS-C as defined by the ROME II criteria. To be eligible, recruited patients also had to report less than three SBMs per week in addition to one or more of lumpy or hard stools, straining or a sensation of incomplete evacuation for at least 25% of bowel movements. The mean age of patients was 44 years and 92% were women. Patients were randomized to receive linaclotide 75, 150, 300 or 600 μg, or placebo, once daily for 12 weeks. The primary endpoint was the change in the number of CSBMs per week from baseline. Secondary endpoints included effect on individual symptoms

and quality of life, as well as the proportion of patients who were CSBM responders, defined as a patient with a weekly CSBM rate of at least three and an increase of at least one from baseline for 9 of the 12 weeks of therapy, the proportion who were adequate relief responders, defined as reporting adequate relief of symptoms for 9 of 12 weeks, and the proportion who were global relief responders, defined as symptoms being somewhat, considerably or completely relieved for all 12 weeks, or completely relieved for 6 of 12 weeks.

The mean change in the number of CSBMs per week for placebo was 1.01. For 75, 150, 300 and 600 μg the mean change in CSBMs per week was 2.90, 2.49, 3.61 and 2.68 respectively ($p < 0.01$ for all linaclotide doses compared with placebo). Stool consistency, straining and abdominal pain scores were significantly improved with all doses of linaclotide compared with placebo. Differences in quality of life scores, however, were not significantly different. The proportion of patients who were CSBM responders with placebo was 12% compared with 25%, 19.5%, 32% and 24% with 75, 150, 300 and 600 μg linaclotide. These differences were statistically significant for all linaclotide doses, except the 150 μg dose. Significantly higher proportions of patients receiving linaclotide (33–51%) were adequate relief responders compared with placebo (22%). Response rates for global relief were 44–58% with linaclotide *versus* 29% with placebo.

Rates of diarrhoea ranged between 11.4% of patients in the 75 μg arm and 18.0% in the 600 μg arm compared with 1.2% in the placebo group. Of those experiencing diarrhoea, 13 patients in the linaclotide arms discontinued therapy as a result. There were no cases of dehydration or electrolyte disturbance.

Phase III studies

Two phase III randomized, double-blind, placebo-controlled trials were published in 2012 [Chey *et al.* 2012; Rao *et al.* 2012]. The first of these was conducted in 102 centres in the USA and randomized 804 patients to receive linaclotide 290 μg or placebo for 26 weeks [Chey *et al.* 2012]. Inclusion criteria were similar to the aforementioned phase IIb trial. The mean age of included patients was 40 years and 90% were women.

Primary endpoints were based on US Food and Drug Agency (FDA) guidance for IBS trials developed in 2012. An FDA responder was defined as a patient who had an improvement of at least 30% from baseline in the average of the daily worst abdominal score, and an increase of at least one CSBM from baseline. Both needed to occur in the same week for at least 6 of the first 12 weeks of the treatment period. Other primary endpoints included an improvement of at least 30% from baseline in the weekly average of the daily worst abdominal pain scores, at least three CSBMs with an increase of at least one CSBM from baseline for at least 9 of the first 12 weeks of therapy, and finally a combination of the previous two points with a responder defined as a patient meeting both of the above in the same week. Key secondary endpoints included effect on abdominal pain, abdominal discomfort, bloating, stool frequency and consistency, and straining.

The European Medicines Agency (EMA) set slightly different primary endpoints [Quigley *et al.* 2013]. An abdominal pain or discomfort responder was required to experience a 30% reduction in mean abdominal pain or discomfort score on an 11-point scale, with neither condition worsening from baseline for at least 6 weeks, and a 12-week IBS degree of relief responder was required to report that symptoms were considerably or completely relieved for at least 6 weeks.

For all the primary endpoints, linaclotide 290 μg showed statistically significant improvements compared with placebo. For the first 12 weeks, 34% of patients receiving linaclotide met the FDA combined primary endpoint compared with 14% for placebo ($p < 0.001$). The number needed to treat for the primary endpoint was five. When symptom data over 9 of 12 weeks were examined, 18% of patients receiving linaclotide met criteria for response *versus* 5% of patients on placebo. When the combined endpoint was studied, 13% of patients receiving linaclotide were classified as responders compared with 3% of those assigned to placebo. Over the entire 26-week treatment period, 32% and 13% of patients receiving linaclotide and placebo respectively met the FDA endpoint for a minimum of 13 weeks out of the 26-week trial. Finally, improvements in abdominal pain, abdominal discomfort, bloating, stool frequency and consistency, and straining scores were all significantly greater with linaclotide over 12 and 26 weeks of therapy. The EMA responder endpoints were also met by significantly more patients receiving linaclotide [Quigley *et al.* 2013].

Total numbers of adverse events were significantly higher among linaclotide-treated patients, occurring in 65.4% compared with 56.6% ($p < 0.05$). However, most were mild or moderate in severity. Once again, the most common adverse event reported was diarrhoea, occurring in 19.7% of patients randomized to linaclotide, compared with only 2.5% of placebo patients. This resulted in cessation of linaclotide therapy in 4.5% of patients compared with 0.2% in patients receiving placebo.

The second phase III trial differed in terms of its design in that patients were randomized to receive linaclotide 290 μg or placebo for a total of 12 weeks, followed by a 4-week randomized withdrawal period [Rao *et al.* 2012]. However, inclusion criteria and endpoints were identical to the first trial. The mean age of the 800 participants was 43.5 and 90% were women. Among patients randomized to receive linaclotide, 34% met the FDA endpoint compared with 21% assigned to placebo ($p < 0.001$). The number needed to treat for the primary endpoint was 8. A statistically significantly higher number of patients also met criteria for the other primary endpoints and secondary endpoints. During the 4-week withdrawal period, patients originally randomized to linaclotide who remained on linaclotide showed a continued and sustained response whilst those rerandomized to placebo demonstrated an increase in symptoms of abdominal pain and a decrease in CSBM frequency to the level of those reported by the placebo arm of the trial during the first 12 weeks of therapy. Again, significantly more patients receiving linaclotide met the EMA responder endpoints [Quigley *et al.* 2013].

The total numbers of adverse events and serious adverse events were not significantly higher among patients receiving linaclotide in this trial (56.2% *versus* 53.0%). However, diarrhoea was again the predominant side effect experienced, with 19.5% of patients receiving linaclotide reporting diarrhoea compared with 3.5% of patients on placebo. Overall, 7.9% of patients taking linaclotide discontinued the drug as a result of any of the adverse events compared with 2.8% of patients on placebo.

Conclusion

While treatment goals in CIC and IBS-C may be different, linaclotide follows other drugs that have proved to be beneficial for the treatment of both conditions, including tegaserod [Evans *et al.* 2007; Ford *et al.* 2009a], which was withdrawn by the FDA in 2007 [FDA, 2007] and lubiprostone [Drossman *et al.* 2009; Johanson *et al.* 2008]. This underlines the potential for overlap in underlying pathophysiological mechanisms between CIC and IBS-C. Data from randomized placebo-controlled trials demonstrate that linaclotide is effective across a wide range of endpoints studied (see Table 1), with numbers needed to treat of between 5 and 8, and the drug has been approved for the treatment of both conditions in the USA, and for the treatment of IBS-C in Europe. Adverse events have been, for the most part, no more frequent with linaclotide compared with placebo, although diarrhoea appears to be an issue. Electrolyte disturbances and dehydration have not been reported. It should be noted that the drug has been tested mainly in women, with 88–100% of trial participants being women, and therefore its efficacy in men with CIC and IBS-C is less clear.

While linaclotide is a first-in-class drug, plecanatide, another drug with the same mechanism of action, is undergoing preliminary trials in CIC and IBS-C. Plecanatide appeared to be effective in a phase IIa placebo-controlled trial in CIC [Shailubhai *et al.* 2011] and the authors reported that diarrhoea did not occur with the active drug in any of the recruited patients. A phase IIb/III trial randomizing over 800 patients with CIC to plecanatide or placebo has been completed recently, with the results expected soon, and a phase II placebo-controlled trial in IBS-C is ongoing.

Despite the efficacy of linaclotide in placebo-controlled trials in CIC, as yet, there are no head-to-head trials against other less expensive and more well established treatments. Laxatives, such as bisacodyl, sodium picosulfate and polyethylene glycol (PEG) are also effective for the treatment of CIC [Ford and Suares, 2011]. In a recent randomized noninferiority trial comparing PEG with prucalopride, a drug acting on the 5-hydroxytryptamine receptor agonist licensed for the treatment of CIC in women, PEG was equally effective and appeared to be better tolerated [Cinca *et al.* 2013]. Therefore, before the place of linaclotide in the treatment pathway of CIC is clear, randomized controlled trials of the drug *versus* current accepted treatments will be required to assess efficacy, cost effectiveness and safety. However, in IBS-C, where there are no other licensed drugs

currently available, linaclotide represents a promising new therapy.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

Ruchit Sood has no conflicts of interest to declare. Alexander C. Ford has received research funding from Almirall.

References

Andresen, V., Camilleri, M., Busciglio, I., Grudell, A., Burton, D., Mckinzie, S. *et al.* (2007) Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. *Gastroenterology* 133: 761–768.

Busby, R., Bryant, A., Bartolini, W., Cordero, E., Hannig, G., Kessler, M. *et al.* (2010). Linaclotide, through activation of guanylate cyclase C, acts locally in the gastrointestinal tract to elicit enhanced intestinal secretion and transit. *Eur J Pharmacol* 15: 328–335.

Chang, J., Locke, G., III, Mcnally, M., Halder, S., Schleck, C., Zinsmeister, A. *et al.* (2010) Impact of functional gastrointestinal disorders on survival in the community. *Am J Gastroenterol* 105: 822–832.

Chey, W., Lembo, A., Lavins, B., Shiff, S., Kurtz, C., Currie, M. *et al.* (2012) Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol* 107: 1702–1712.

Cinca, R., Chera, D., Gruss, H. and Halphen, M. (2013) Randomised clinical trial: macrogol/PEG 3350+electrolytes versus prucalopride in the treatment of chronic constipation – a comparison in a controlled environment. *Aliment Pharmacol Ther* 37: 876–886.

Drossman, D., Chey, W., Johanson, J., Fass, R., Scott, C., Panas, R. *et al.* (2009) Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome – results of two randomized, placebo-controlled studies. *Aliment Pharmacol Ther* 29: 329–341.

Drossman, D., Whitehead, W., Toner, B., Diamant, N., Hu, Y., Bangdiwala, S. *et al.* (2000) What determines severity amongst patients with painful functional bowel disorders? *Am J Gastroenterol* 95: 974–980.

Eutamene, H., Bradesi, S., Larauche, M., Theodorou, V., Beaufrand, C., Ohning, G. *et al.* (2010) Guanylate cyclase-C mediated antinociceptive effects of linaclotide in rodent models of visceral pain. *Neurogastroenterol Motil* 22: 312–e84.

Evans, B., Clark, W., Moore, D. and Whorwell, P. (2007) Tegaserod for the treatment of irritable bowel syndrome and chronic constipation. *Cochrane Database Syst Rev* (4): CD003960.

FDA (2007) Public Health Advisory: tegaserod maleate (marketed as Zelnorm). Available at: http://www.fda.gov/cder/drug/advisory/tegaserod.htm (accessed 15 May 2013).

Ford, A., Brandt, L., Young, C., Chey, W., Foxx-Orenstein, A. and Moayyedi, P. (2009a) Efficacy of 5-HT_3 antagonists and 5-HT_4 agonists in irritable bowel syndrome: systematic review and meta-analysis. *Am J Gastroenterol* 104: 1831–1843.

Ford, A., Forman, D., Bailey, A., Axon, A. and Moayyedi, P. (2012) Effect of dyspepsia on survival: a longitudinal 10-year follow-up study. *Am J Gastroenterol* 107: 912–921.

Ford, A., Marwaha, A., Lim, A. and Moayyedi, P. (2010) Systematic review and meta-analysis of the prevalence of irritable bowel syndrome in individuals with dyspepsia. *Clin Gastroenterol Hepatol* 8: 401–409.

Ford, A. and Suares, N. (2011) Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. *Gut* 60: 209–218.

Ford, A., Talley, N., Schoenfeld, P., Quigley, E. and Moayyedi, P. (2009b) Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. *Gut* 58: 367–378.

Ford, A., Talley, N., Spiegel, B., Foxx-Orenstein, A., Schiller, L., Quigley, E. *et al.* (2008) Effect of fibre, antispasmodics, and peppermint oil in irritable bowel syndrome: systematic review and meta-analysis. *Br Med J* 337: 1388–1392.

Johanson, J., Morton, D., Geene, J. and Ueno, R. (2008) Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. *Am J Gastroenterol* 103: 170–177.

Johnston, J., Kurtz, C., Drossman, D., Lembo, A., Jeglinski, B., MacDougall, J. *et al.* (2009) Pilot study on the Effects of linaclotide in patients with chronic constipation. *Am J Gastroenterol* 104: 125–132.

Johnston, J., Kurtz, C., MacDougall, J., Lavins, B., Currie, M., Fitch, D. *et al.* (2010) Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome and constipation. *Gastroenterology* 139: 1877–1886.

Lembo, A., Kurtz, C., MacDougall, J., Lavins, B., Currie, M., Fitch, D *et al.* (2010) Efficacy of linaclotide for patients with chronic constipation. *Gastroenterology* 138: 886–895.

Lembo, A., Schneier, H., Shiff, S., Kurtz, C., MacDougall, J., Jia, X. *et al.* (2011) Two randomized trials of linaclotide for chronic constipation. *N Engl J Med* 365: 527–536.

Longstreth, G., Thompson, W., Chey, W., Houghton, L., Mearin, F. and Spiller, R. (2006) Functional bowel disorders. *Gastroenterology* 130: 1480–1491.

Lovell, R. and Ford, A. (2012a) Prevalence of gastro-esophageal reflux-type symptoms in individuals with irritable bowel syndrome in the community: a meta-analysis. *Am J Gastroenterol* 107: 1793–1801.

Lovell, R. and Ford, A. (2012b) Effect of gender on prevalence of irritable bowel syndrome in the community: systematic review and meta-analysis. *Am J Gastroenterol* 107: 991–1000.

Lovell, R. and Ford, A. (2012c) Global prevalence of, and risk factors for, irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol* 10: 712–721.

Maxion-Bergemann, S., Thielecke, F., Abel, F. and Bergemann, R. (2006) Costs of irritable bowel syndrome in the UK and US. *Pharmacoeconomics* 24: 21–37.

Moayyedi, P., Ford, A., Brandt, L., Foxx-Orenstein, A., Cremonini, F., Talley, N. *et al.* (2010) The efficacy of probiotics in the treatment of irritable bowel syndrome: a systematic review. *Gut* 59: 325–332.

Peery, A., Dellon, E., Lund, J., Crockett, S., McGowan, C., Bulsiewicz, W. *et al.* (2012) Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology* 143: 1179–1187.

Quigley, E., Tack, J., Chey, W., Rao, S., Fortea, J., Falques, M. *et al.* (2013) Randomised clinical trials: linaclotide phase 3 studies in IBS-C – a prespecified further analysis based on European Medicines Agency-specified endpoints. *Aliment Pharmacol Ther* 37: 49–61.

Rao, S., Lembo, A., Shiff, S., Lavins, B., Currie, M., Jia, X. *et al.* (2012) 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* 107: 1714–1724.

Shailubhai, K., Barrow, L., Talluto, C., Comiskey, S., Foss, J., Feng, R. *et al.* (2011) Plecanatide, a guanylate cyclase C agonist improves bowel habits and symptoms associated with chronic constipation in a phase IIa clinical study. *Am J Gastroenterol* 106(Suppl. 2s): S502.

Suares, N. and Ford, A. (2011a) Systematic review: the effects of fibre in the management of chronic idiopathic constipation. *Aliment Pharmacol Ther* 33: 895–901.

Suares, N. and Ford, A. (2011b) Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. *Am J Gastroenterol* 106: 1582–1591.

Wald, A., Scarpignato, C., Kamm, M., Mueller-Lissner, S., Helfrich, I., Schuijt, C. *et al.* (2007) The burden of chronic constipation on quality of life: results of a multinational survey. *Aliment Pharmacol Ther* 26: 227–236.

Wong, R., Palsson, O., Turner, M., Levy, R., Feld, A., Von Korff, M. *et al.* (2010) Inability of the Rome III criteria to distinguish functional constipation from constipation-subtype irritable bowel syndrome. *Am J Gastroenterol* 105: 2228–2234.