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Randomised clinical trials: linaclotide phase 3 studies in IBS-C – a prespecified further analysis based on European Medicines Agency-specified endpoints

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SUMMARY

Background
Treatment options that improve overall symptoms of irritable bowel syndrome with constipation (IBS-C) are lacking.

Aim
A prespecified further analysis to evaluate the efficacy and safety of linaclotide, a guanylate cyclase C agonist, in patients with IBS-C, based on efficacy parameters prespecified for European Medicines Agency (EMA) submission.

Methods
Two randomised, double-blind, multicentre Phase 3 trials investigated once-daily linaclotide (290 μg) for 12 weeks (Trial 31) or 26 weeks (Trial 302) in patients with IBS-C. Prespecified primary endpoints were the EMA-recommended co-primary endpoints: (i) 12-week abdominal pain/discomfort responders [$\geq$30% reduction in mean abdominal pain and/or discomfort score (11-point scales), with neither worsening from baseline, for $\geq$6 weeks] and (ii) 12-week IBS degree-of-relief responders (symptoms 'considerably' or 'completely' relieved for $\geq$6 weeks).

Results
Overall, 803 (Trial 31) and 805 patients (Trial 302) were randomised. A significantly greater proportion of linaclotide-treated vs. placebo-treated patients were 12-week abdominal pain/discomfort responders (Trial 31: 54.8% vs. 41.8%; Trial 302: 54.1% vs. 38.5%; $P < 0.001$) and IBS degree-of-relief responders (Trial 31: 37.0% vs. 18.5%; Trial 302: 39.4% vs. 16.6%; $P < 0.0001$). Similarly, significantly more linaclotide- vs. placebo-treated patients were responders for $\geq$13 weeks in Trial 302 (abdominal pain/discomfort: 53.6% vs. 36.0%; IBS degree-of-relief: 37.2% vs. 16.9%; $P < 0.0001$). The proportion of sustained responders (co-primary endpoint responders plus responders for $\geq$2 of the last 4 weeks of treatment) was also significantly greater with linaclotide vs. placebo in both trials ($P < 0.001$).

Conclusion
Linaclotide treatment significantly improved abdominal pain/discomfort and degree-of-relief of IBS-C symptoms compared with placebo over 12 and 26 weeks. Trial registration: ClinicalTrials.gov (identifiers: NCT00948818 and NCT00938717).

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INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic, gastrointestinal disorder that affects approximately 10–15% of the population in Europe.[1–3] It is characterised by recurrent abdominal pain or discomfort associated with defaecation or a change in bowel habit and is commonly accompanied by features of disordered defaecation.[4, 5] IBS can have a considerable impact on patient quality of life and is associated with a substantial economic burden of care, both in terms of healthcare resource utilisation and work productivity.[1, 6–9]

Approximately one-third of patients with IBS experience constipation as their predominant bowel symptom [IBS with constipation (IBS-C) subtype].[3, 10] As with all IBS subtypes, there is no gold standard of therapy for IBS-C and currently available treatment options tend to focus on the relief of individual symptoms.[11] While traditional therapies, such as fibre and laxatives, may improve constipation, they can aggravate bloating and generally have little impact on abdominal symptoms or overall symptom relief in comparison with placebo.[12] More recently, serotonin reuptake inhibitors and serotonergic agents have shown promise in IBS-C, but a variable magnitude of effect and/or tolerability issues have limited their widespread use.[13, 14] For example, tegaserod, a 5-hydroxytryptamine receptor agonist, demonstrated efficacy for the overall relief of IBS-C symptoms in addition to improving abdominal pain/discomfort, bloating and constipation,[15] but as a result of cardiovascular safety concerns, was withdrawn from the market in the United States[16] and was not approved in the European Union. Thus, there remains an unmet need for well-tolerated and effective therapies that relieve all IBS-C symptoms, including abdominal pain and other associated abdominal symptoms, in addition to improving bowel function.

In spite of our increasing understanding of the heterogeneous pathophysiology of this multifaceted disease, the development of new IBS treatments remains challenging.[17–19] The assessment of treatment outcomes in clinical trials has been based on patient ratings of symptom severity using a variety of endpoints and questionnaires, and in the absence of an instrument that adequately assesses all the clinically important symptoms of IBS, regulatory bodies, including both the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have developed separate guidelines for the design of Phase 3 clinical trials. These include recommended endpoints to support labelling claims for what they each consider to be the most important IBS symptoms. For IBS-C, the FDA recommends combined responder endpoints that capture abdominal pain and constipation, whereas the EMA recommends co-primary responder endpoints that capture abdominal pain/discomfort along with an assessment of change in overall symptoms.[17, 18] As a result of the differences in endpoints recommended for inclusion in clinical trials by the FDA and EMA, all endpoints relevant to either regulatory body, with separate statistical analysis plans, are required if clinical trials are to provide the data necessary for registration in different countries.

Linaclotide, a first-in-class guanylate cyclase C agonist (GCCA), is a new therapy in development for IBS-C. By binding to guanylate cyclase C receptors on the luminal surface of gastrointestinal epithelial cells, linaclotide stimulates intracellular production of cyclic guanosine monophosphate (cGMP), resulting in chloride and bicarbonate secretion into the gastrointestinal lumen and, consequently, increased fluid secretion and accelerated intestinal transit.[20–22] Linaclotide has also been shown to reduce visceral hypersensitivity in animal models, which may be related to cGMP modulation of afferent nerve activity.[20–22] In Phase 2 studies, linaclotide accelerated colonic transit and emptying, improved bowel function (including bowel movement frequency, stool consistency and severity of straining) and reduced abdominal pain severity, compared with placebo, in patients with IBS-C.[23, 24]

The efficacy and safety of linaclotide in patients with IBS-C has been further evaluated in two randomised, placebo-controlled Phase 3 trials. These trials were designed in accordance with both FDA and EMA guidelines for the clinical investigation of therapies for IBS, and findings based on FDA-recommended endpoints have been reported elsewhere.[25, 26] In this paper, we report the findings of a planned, separate analysis of both trials based on the distinct efficacy parameters prespecified for EMA submission.

MATERIALS AND METHODS

Trial design

Two randomised, double-blind, placebo-controlled, parallel-group, multicentre Phase 3 trials (Trial 31, NCT00948818 and Trial 302, NCT00938717) were conducted in the United States and Canada between July 2009 and September 2010. The methodology and findings of these trials, and the safety and efficacy outcomes according to FDA-recommended endpoints have been published in detail elsewhere.[25, 26] Trial 31 was

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conducted at 118 out-patient clinical research centres (111 in the United States, 7 in Canada). Trial 302 was conducted in 102 centres in the United States.

Patients, aged at least 18 years, with IBS-C (modified Rome II criteria) and a mean daily abdominal pain score of at least 3.0 [11-point numerical rating scale (NRS)] during the 2 weeks prior to starting treatment were equally randomised to receive linaclotide 290 μg or placebo once daily for 12 weeks (Trial 31) or 26 weeks (Trial 302). Abdominal symptoms (pain, discomfort and bloating) and bowel function symptoms (spontaneous bowel movement frequency, complete spontaneous bowel movement frequency, stool consistency and severity of straining) were assessed daily throughout the trials by calls to an interactive voice response system (IVRS). Safety assessments included adverse event (AE) monitoring, clinical laboratory tests, electrocardiogram recordings, vital sign measurements and physical examinations.

Both trials were conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. The protocols were approved by institutional review boards at each trial centre and all patients provided informed consent before participating in any trial procedures.

EMA analysis endpoints

A prespecified analysis of both trials, separate from the previously reported FDA analyses,[25, 26] was conducted for EMA submission and assessed abdominal pain, abdominal discomfort and degree-of-relief of IBS-C symptoms. The two co-primary efficacy parameters evaluated in this analysis, based on EMA recommendations, were 12-week abdominal pain/discomfort responders and 12-week IBS degree-of-relief responders.

Abdominal pain and abdominal discomfort were each individually assessed daily using an 11-point NRS, whereby patients were asked to rate their worst abdominal pain and their abdominal discomfort over the last 24 h on a scale from '0' (none) to '10' (very severe). A 12-week abdominal pain/discomfort responder was a patient who, for at least 6 weeks out of the first 12 weeks of treatment, had an improvement of 30% or more from baseline in either mean worst abdominal pain score or mean abdominal discomfort score for that week, with neither of these scores worsening from baseline for that week. In contrast with the FDA-recommended primary combined responder endpoint, which includes assessment of abdominal pain, the EMA-recommended co-primary endpoint includes both abdominal pain and discomfort, and is more closely aligned with the Rome diagnostic criteria for IBS.[4]

Patient assessment of degree-of-relief of IBS symptoms was recorded weekly via IVRS calls. Patients were asked to rate their IBS symptoms during the past 7 days compared with before the trial started using a 7-point balanced ordinal scale, where '1' indicated 'completely relieved', '4' indicated 'unchanged' and '7' indicated 'as bad as I can imagine'. A 12-week IBS degree-of-relief responder was a patient whose response to the degree-of-relief of IBS symptoms question was 'considerably relieved' or 'completely relieved' (i.e. a score of 1 or 2) for at least 6 weeks out of the first 12 weeks of treatment.

In Trial 302, 26-week abdominal pain/discomfort responders and 26-week IBS degree-of-relief responders (responders for at least 13 out of 26 weeks of treatment) were also assessed as EMA-recommended secondary endpoints. In both trials, sustained responder criteria were defined as additional EMA-recommended efficacy endpoints. Sustained responders were patients who met the co-primary endpoints and were also responders for at least 2 of the last 4 weeks of treatment.

Further EMA-recommended additional endpoints to assess health outcomes included the Irritable Bowel Syndrome-Quality of Life (IBS-QoL)[27] and EuroQoL-5 Dimensions (EQ-5D) instruments.[28] IBS-QoL was self-administered at baseline, at Week 12 and at the end of treatment, and comprised an overall average score plus eight subscale scores (dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual and relationships). EQ-5D, self-administered at baseline and at all subsequent visits, assessed the following aspects of health status: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Responses on each of these subscales were converted to a corresponding utility index. In a second EQ-5D component, patients rated their health state from '0' (worst imaginable) to '100' (best imaginable) using a visual analogue scale (EQ-5D VAS).

Other symptoms that were assessed as secondary endpoints for the EMA analysis – stool frequency, stool consistency, severity of straining and abdominal bloating – were also secondary endpoints for the FDA submission. The changes from baseline to Week 12 in these symptoms have been previously reported in detail.[25, 26]

Statistical analysis

All EMA efficacy endpoint analyses for both trials were based on the intent-to-treat (ITT) population, which

included all randomised patients who received at least one dose of trial drug and who completed at least one post-randomisation primary efficacy assessment. For both trials, the proportion of abdominal pain/discomfort and IBS degree-of-relief responders in each treatment group was compared using a Cochran-Mantel–Haenszel test controlling for geographic region. The differences in responder rates, corresponding 95% confidence intervals (CIs) and two-sided *P*-values were calculated. The overall type I family-wise error rates for testing the co-primary and the main secondary efficacy parameters were controlled at the 0.05 significance level using a three-step serial gate-keeping, multiple comparisons procedure. An observed case approach to missing data was applied for responder variables and continuous efficacy variables: if a patient did not have a score (responder/nonresponder) for a particular Treatment Period week, the patient was not considered a responder for that Treatment Period week. This approach is conservative and any bias is against treatment. A sensitivity analysis was conducted using the last observation carried forward (LOCF) technique, which confirmed the robustness of the study results.

IBS-QoL overall and subscale scores, and EQ-5D utility score and VAS were summarised descriptively by treatment group (mean, standard deviation, standard error, median, range). Changes from baseline to Week 12 were analysed using an analysis of covariance (ANCOVA) model that used treatment group and geographical region as fixed effects and baseline values as a covariate. Least squares (LS) mean changes from baseline for each treatment group, difference in LS mean changes between the linaclotide and placebo groups, corresponding CIs, and two-sided *P*-values were calculated. The LOCF approach was used to impute missing values; LOCF is an accepted and typically used method for QoL variables, and no bias in the results is to be expected.

Weekly change from baseline was analysed longitudinally using a generalised linear model, based on the observed cases during the Treatment Period; treatment group, geographical region, week, week by treatment interaction and subject were fixed effects and baseline values were a covariate.

RESULTS

Patients

In Trial 31, 2424 patients were screened, 803 patients randomised, 802 treated and 800 included in the ITT population (linaclotide $n = 405$; placebo $n = 395$). The 12-week Treatment Period was completed by 647 patients. In Trial 302, 2340 patients were screened, 805 patients randomised and treated, and 804 included in the ITT population (linaclotide $n = 401$; placebo $n = 403$). The first 12 weeks of the Treatment Period were completed by 655 patients and 599 completed 26 weeks of treatment. The most common reasons for treatment discontinuation were adverse events and withdrawal of consent for the linaclotide group in both trials. In the placebo groups, the most common reasons for discontinuation were withdrawal of consent and adverse events in Trial 31, and insufficient therapeutic response and withdrawal of consent in Trial 302. The discontinuation rate was similar to that seen in other trials in patients with IBS-C. Full details of reasons for and numbers of discontinuations have been reported previously.[25, 26]

Overall, the majority of patients were female (approximately 90%) and white (77–78%). Mean age was 43.5 years in Trial 31 and 44.3 years in Trial 302. Demographics and baseline characteristics were similar between treatment groups in both trials and are detailed elsewhere.[25, 26]

Abdominal pain/discomfort responders

A significantly greater proportion of patients treated with linaclotide were 12-week abdominal pain/discomfort responders (co-primary endpoint) compared with those treated with placebo in both trials (Trial 31: 54.8% vs. 41.8%, $P < 0.001$; Trial 302: 54.1% vs. 38.5%, $P < 0.0001$) (Figure 1a). In addition, in both trials, an increase in the proportion of weekly responders was observed after 1 week in all treatment groups; this response rate was generally maintained throughout the Treatment Periods, and was significantly greater in the linaclotide groups vs. corresponding placebo groups (Figure 2).

In Trial 302, the proportion of 26-week abdominal pain/discomfort responders in both treatment groups was similar to that observed during the first 12 weeks of the Treatment Period and was significantly higher in the linaclotide group vs. the placebo group (53.6% vs. 36.0%, $P < 0.0001$) (Figure 3a).

IBS degree-of-relief responders

The proportion of patients who were 12-week IBS degree-of-relief responders (co-primary endpoint) was significantly higher in the linaclotide treatment groups than in the placebo treatment groups of both trials (Trial 31: 37.0% vs. 18.5%, $P < 0.0001$; Trial 302: 39.4% vs. 16.6%, $P < 0.0001$) (Figure 1b).

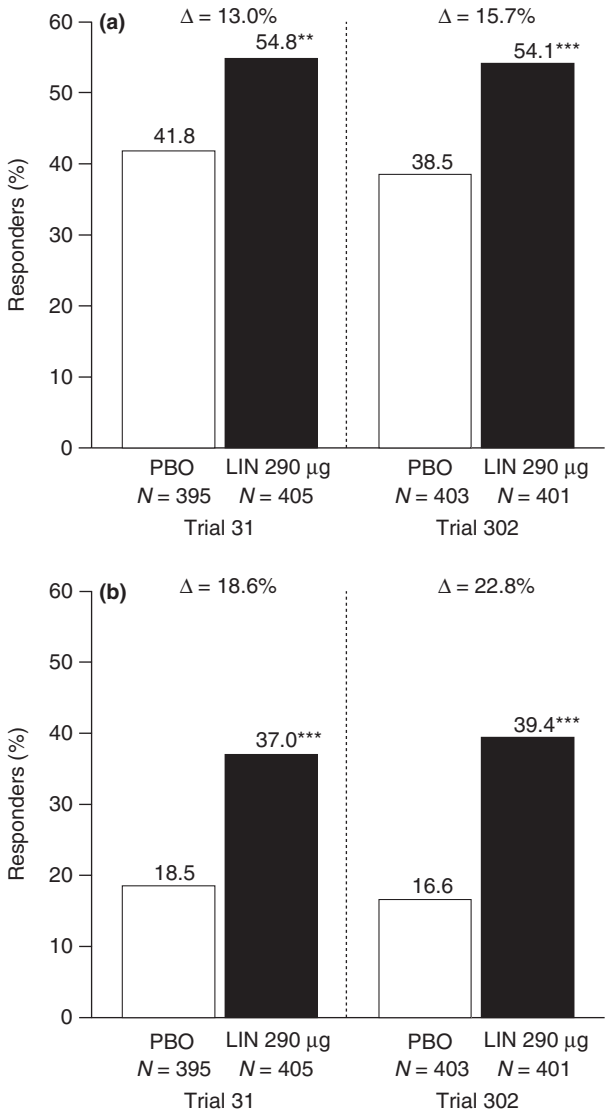

Figure 1 | Proportion of patients in each treatment group who were (a) 12-week abdominal pain/discomfort responders and (b) 12-week degree-of-relief responders in Trial 31 and 302 (ITT population; observed cases). $^{**}P < 0.001$; $^{***}P < 0.0001$ (LIN versus PBO, CMH test). CMH, Cochran-Mantel–Haenszel test; IBS, irritable bowel syndrome; ITT, intent-to-treat; LIN, linaclotide; PBO, placebo.

In Trial 31, an increase in the proportion of IBS degree-of-relief weekly responders was observed with linaclotide and placebo after 1 week of treatment (23.0% and 8.9%, respectively, $P < 0.0001$ CMH test), with the responder rate generally maintained throughout the 12-week Treatment Period and significantly greater with linaclotide vs. placebo at each week. A similar pattern of significantly greater responder rate with linaclotide vs. placebo was observed over the first 12 weeks of the Treatment Period in Trial 302. In Trial 302, the 26-week IBS degree-of-relief responder rate for both treatment groups was similar to the 12-week responder rate and was significantly higher in the linaclotide group vs. the placebo group (37.2% vs. 16.9%, $P < 0.0001$) (Figure 3b).

Sustained responders

In both trials, the proportion of patients who met the criteria for 12-week abdominal pain/discomfort and IBS degree-of-relief sustained response (i.e. were 12-week responders and also responders for at least 2 of the last 4 weeks of treatment) was similar to the proportion of patients who met the co-primary endpoint criteria.

Compared with placebo, a significantly greater proportion of patients treated with linaclotide were 12-week abdominal pain/discomfort sustained responders in both Trial 31 (53.1% vs. 41.5%, $P \leq 0.001$) and in Trial 302 (53.6% vs. 38.0%, $P < 0.0001$) (Figure 4a). In Trial 302, 51.9% of linaclotide-treated patients vs. 33.3% of placebo-treated patients ($P < 0.0001$) were 26-week abdominal pain/discomfort sustained responders (26-week responders plus also responders for at least 2 of the last 4 weeks of treatment) (Figure 4a).

In comparison with placebo, a significantly greater proportion of patients treated with linaclotide vs. placebo were 12-week IBS degree-of-relief sustained responders in both Trial 31 (33.8% vs. 18.2%, $P < 0.0001$) and Trial 302 (36.7% vs. 15.6%, $P < 0.0001$) (Figure 4b). In Trial 302, 33.2% vs. 14.1% of patients treated with linaclotide and placebo, respectively ($P < 0.0001$), were 26-week IBS degree-of-relief sustained responders (Figure 4b).

Secondary endpoints

Compared with placebo, linaclotide was associated with significant improvements from baseline to Week 12 in all additional abdominal and bowel symptoms that were assessed as secondary endpoints in both trials, as reported elsewhere.[25, 26] Data not previously reported from these linaclotide trials are those on weekly change in bloating severity throughout the treatment periods: patients treated with linaclotide reported a significantly greater decrease from baseline in bloating severity vs. placebo over 12 weeks in Trial 31 ($P < 0.0001$) and over 26 weeks in Trial 302 ($P < 0.0001$) (Figure 5).

Health outcomes assessments

Improvements in quality of life, as assessed by arithmetic mean change in IBS-QoL overall score from baseline to Week 12, were greater in the linaclotide treatment

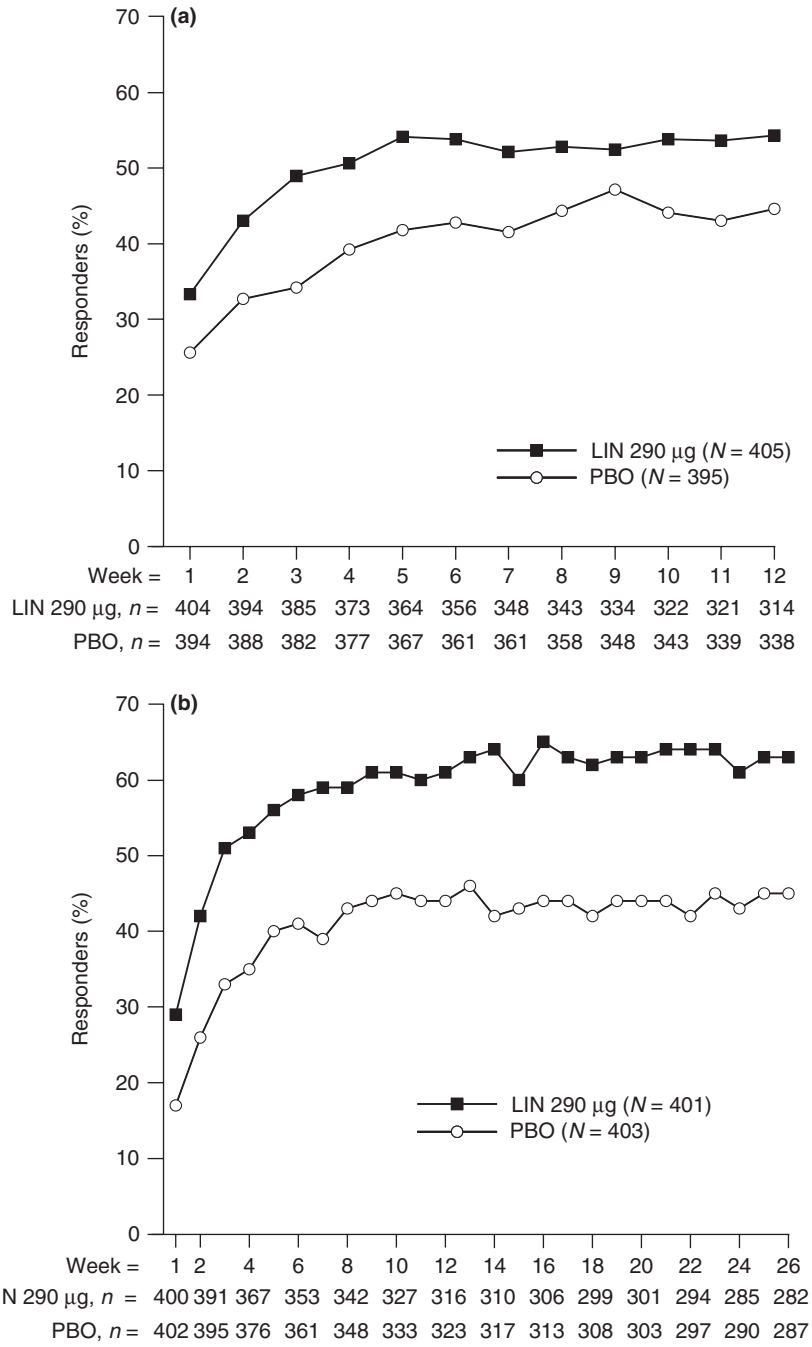

Figure 2 | Abdominal pain/discomfort responders by week in (a) Trial 31 and (b) Trial 302 (ITT population; observed cases). *N* = ITT population; *n* = number of patients with available data. $P < 0.0001$ (LIN vs. PBO, CMH test) at each week of the Treatment Period. CMH, Cochran-Mantel–Haenszel test; ITT, intent-to-treat; LIN, linaclotide; PBO, placebo.

groups of both trials vs. placebo (Figure 6a). In Trial 31, the LS mean change from baseline to Week 12 was 18.4 in the linaclotide group vs. 15.2 in the placebo group [LS mean difference = 3.3 (95% CI: 1.0, 5.5); $P = 0.004$] and in Trial 302, the LS mean change from baseline to Week 12 was 16.6 vs. 11.1 respectively [LS mean difference = 5.5 (95% CI: 3.4, 7.6); $P < 0.0001$]. All IBS-QoL subscales were improved to a significantly greater degree following 12 weeks of treatment with linaclotide compared with placebo in Trial 302. In Trial 31, all subscales showed a significant difference between linaclotide and placebo, with the exception of improvement in the

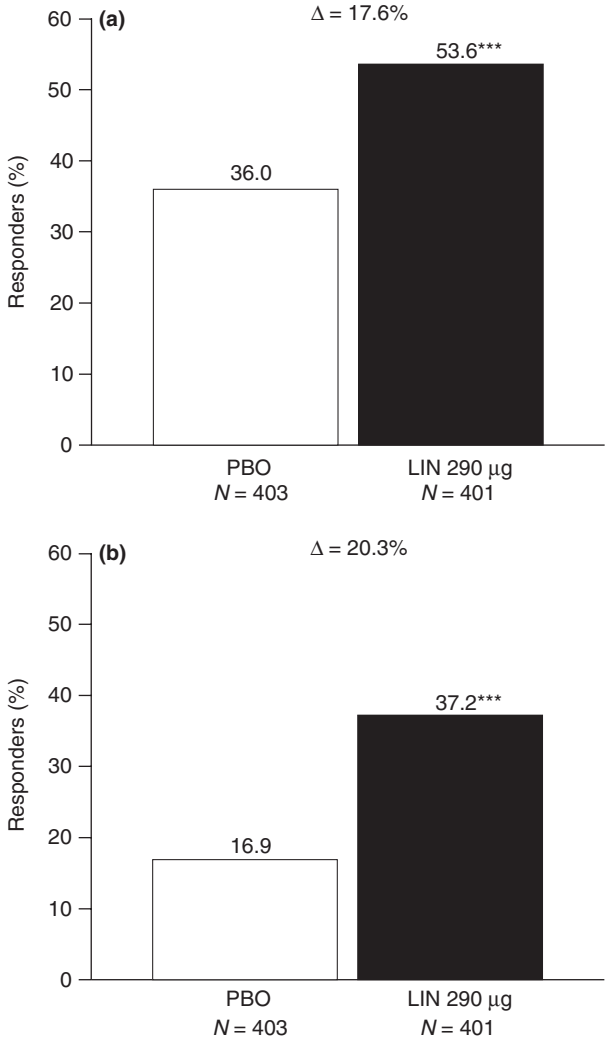

Figure 3 | Proportion of patients in each treatment group who were (a) 26-week abdominal pain/discomfort responders and (b) 26-week IBS degree-of-relief responders in Trial 302 (ITT population; observed cases). ***$P < 0.0001$ (LIN vs. PBO, CMH test). CMH, Cochran-Mantel–Haenszel test; IBS, irritable bowel syndrome; ITT, intent-to-treat; LIN, linaclotide; PBO, placebo.

IBS-QoL interference with activity subscale score ($P = 0.61$) at Week 12 (Table 1).

Linaclotide was also associated with greater improvements in EQ-5D utility index and EQ-5D VAS compared with placebo in both trials, as demonstrated by greater arithmetic mean changes from baseline to Week 12 (Figure 6b–c). Differences between treatment groups for the LS mean change from baseline to Week 12 in EQ-5D utility index were significant in Trial 31 [0.08 vs. 0.05; LS mean difference = 0.03 (95% CI: 0.01, 0.05), $P = 0.001$] and Trial 302 [0.08 vs. 0.04; LS mean difference = 0.03 (95% CI: 0.01, 0.05), $P = 0.0005$]. For EQ-5D VAS, the difference between treatments was significant in Trial 302 [7.1 vs. 4.4; LS mean difference = 2.6 (95% CI: 0.8, 4.5), $P = 0.006$], but not in Trial 31 [5.6 vs. 3.7; LS mean difference = 1.8 (95% CI: −0.1, 3.7), $P = 0.06$].

Safety and tolerability

Safety findings from these trials have been reported in detail elsewhere.[25, 26] In summary, the overall incidence of AEs was 56% and 53% in the linaclotide and placebo groups, respectively, over 12 weeks in Trial 31, and 65% and 57% respectively, over 26 weeks in Trial 302.

Diarrhoea was the most common AE, reported by 19.5% vs. 3.5% of linaclotide- and placebo-treated patients, respectively, over 12 weeks in Trial 31 and by 19.7% vs. 2.5% of patients, respectively, over 26 weeks in Trial 302. Severity was generally mild-to-moderate and relatively few patients who received linaclotide vs. placebo discontinued as a result of diarrhoea (5.7% vs. 0.3% in Trial 31 and 4.5% vs. 0.2% in Trial 302). Serious AEs (SAEs) were experienced by fewer than 2% of patients in either treatment group of both trials and there were no SAEs related to diarrhoea.

DISCUSSION

This prespecified further analysis of two randomised, placebo-controlled Phase 3 trials was planned to evaluate the efficacy and safety of linaclotide in patients with IBS-C based on EMA-recommended endpoints. Our findings, combined with the previously published results from the FDA-recommended endpoints in these trials,[25, 26] consistently demonstrate that treatment with linaclotide was associated with significant and sustained improvements in abdominal, bowel and overall symptoms over 12 and 26 weeks in a typical IBS-C patient population.

EMA guidance for the evaluation of therapies for IBS recommends that change in overall symptoms and in abdominal pain/discomfort should be assessed as co-primary endpoints. To determine efficacy, statistically significant results should be found with both co-primary endpoints.[17] Here, we report that, in comparison with placebo, a significantly greater proportion of patients treated with linaclotide in these two trials met the criteria for abdominal pain/discomfort responders and IBS degree-of-relief responders. The threshold for abdominal pain/discomfort response in the present trials was an improvement of at least 30% from baseline in either score with neither worsening. An improvement in pain intensity score of 30% using an 11-point scale is

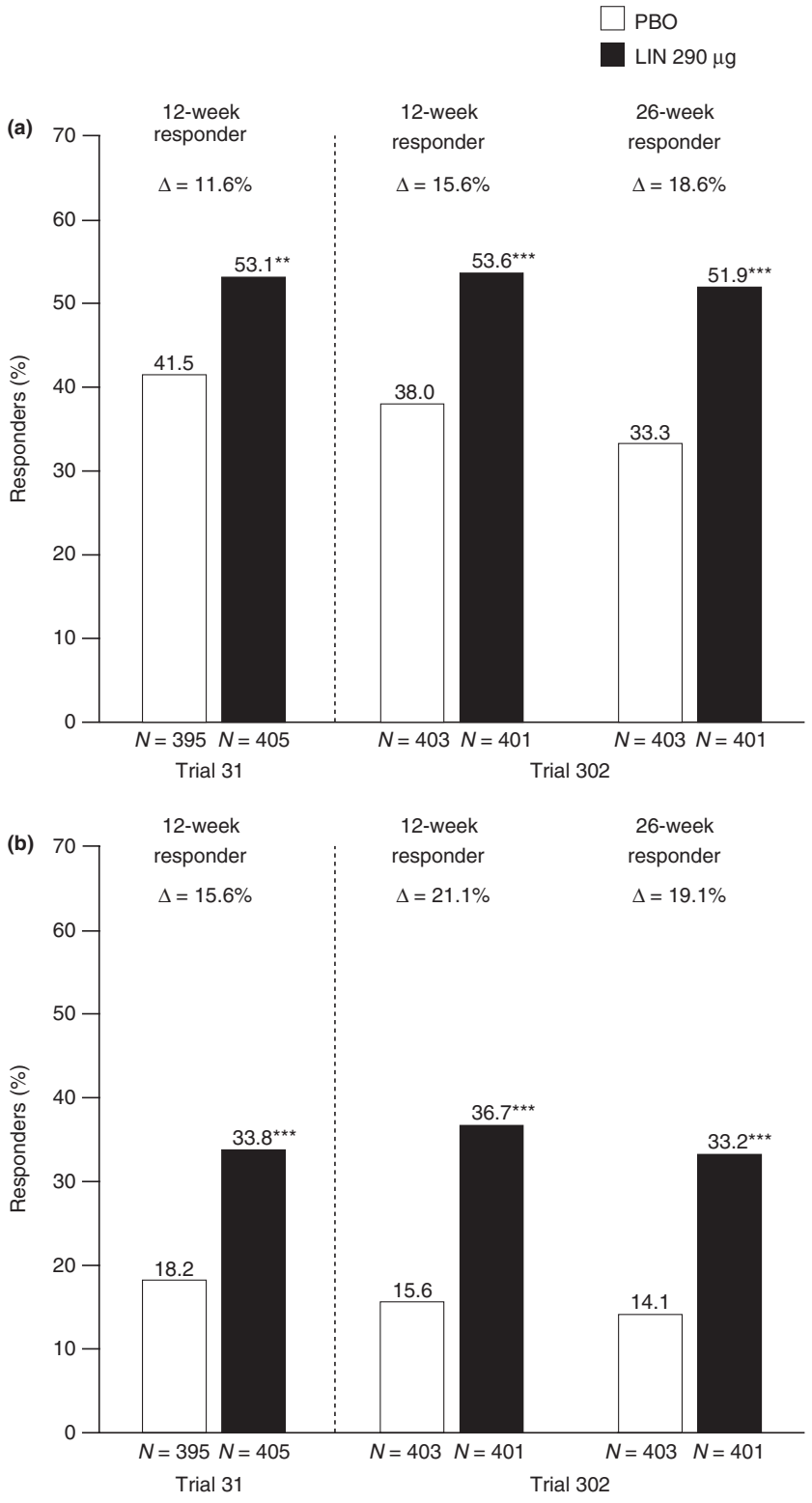

Figure 4 | Proportion of patients in each treatment group who were (a) sustained abdominal pain/discomfort and (b) sustained IBS degree-of-relief responders in Trial 31 and 302 (ITT population; observed cases). $^{**}P < 0.001$; $^{***}P < 0.0001$ (LIN vs. PBO, CMH test). CMH, Cochran-Mantel–Haenszel test; IBS, irritable bowel syndrome; ITT, intent-to-treat; LIN, linaclotide; PBO, placebo.

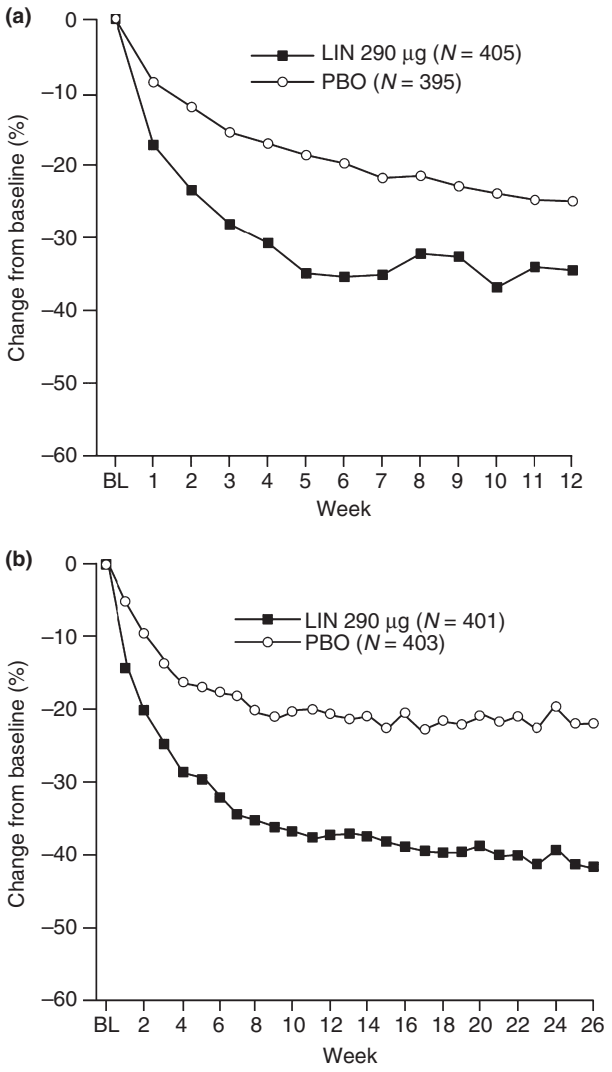

Figure 5 | Weekly change from baseline in bloating severity in (a) Trial 31 and (b) Trial 302 (ITT population, observed cases). Bloating was assessed daily using an 11-point NRS and percent change was calculated as weekly change multiplied by 100 divided by baseline score. $P < 0.0001$ (LIN vs. PBO, generalised linear model ANCOVA). ANCOVA, analysis of covariance; ITT, intent-to-treat; LIN, linaclotide; NRS, numeric rating scale; PBO, placebo.

considered to be a clinically meaningful change, as supported by an examination of the relationship between pain intensity and overall assessments of change in chronic pain trials.[29] Response to linaclotide was sustained throughout both trials, although a decrease in the proportion of patients responding to the weekly IVRS questions at Week 26 led to a lower proportion of IBS degree-of-relief responders at Week 26 in both treatment groups in Trial 302. The reason for patients missing the weekly IVRS questions at Week 26 was due to a methodological limitation allowing patients a 3-day window for clinic visits. Many patients attended the end of trial visit before the last IVRS call (i.e. 1–3 days before the end of the final treatment week). The IVRS was terminated upon the final clinic visit, resulting in missed IBS degree-of-relief assessments for this final treatment week for such patients. Nonetheless, the difference in responder rates between the linaclotide and placebo treatment groups was significant throughout the entire 26-week Treatment Period of Trial 302 for IBS degree-of-relief. The proportion of patients meeting the sustained responder criteria was also significantly higher in the linaclotide groups of both trials vs. placebo. Furthermore, the clinical relevance of the co-primary efficacy findings of the present EMA analysis is supported by the improvements seen in health outcomes, which showed significant improvement for linaclotide compared with placebo in the IBS-QoL overall score and the EQ-5D in both trials.

In separate planned analyses of these trials, linaclotide showed significant improvement over placebo in the FDA-recommended primary combined responder endpoints, which were distinct from the EMA-recommended co-primary endpoints.[25, 26] Linaclotide also showed significant improvements vs. placebo in all secondary abdominal and bowel function parameters, including mean scores for worst abdominal pain score, abdominal discomfort, abdominal bloating, stool consistency and severity of straining and mean number of spontaneous and complete spontaneous bowel movements per week ($P < 0.0001$ in both trials).[25, 26] Furthermore, in Trial 31, patients rerandomised from linaclotide to placebo at the end of the 12-week Treatment Period showed recurrence of symptoms to the level of placebo in the Treatment Period, but no evidence of a rebound effect (i.e. worsening of symptoms compared with baseline).[26]

In addition to the efficacy findings for linaclotide reported here and previously,[25, 26] linaclotide has shown a similar tolerability profile to placebo. In these trials, there were few differences between treatments in the incidence rates for individual AEs with the exception of diarrhoea, which was reported by approximately 20% vs. 3% of patients treated with linaclotide and placebo, respectively.[25, 26] This side effect of treatment was not unexpected, given that linaclotide acts by stimulating the guanylate cyclase C of gastrointestinal epithelial cells to promote cGMP-mediated chloride and bicarbonate secretion into the lumen, resulting in increased fluid secretion and accelerated intestinal transit.[20–22] Most patients who experienced diarrhoea did so within the first week of

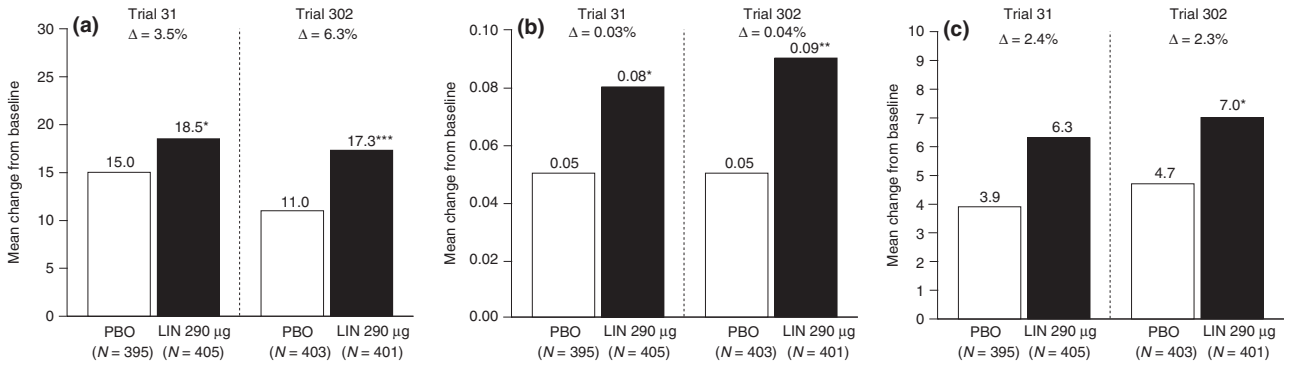

Figure 6 | Improvements in quality of life as assessed by mean changes from baseline to Week 12 in (a) IBS-QoL overall score, (b) EQ-5D utility index and (c) EQ-5D VAS (ITT population, LOCF). $*P < 0.01$; $**P < 0.001$; $***P < 0.0001$. Mean change from baseline are presented with *P*-values derived from ANCOVA on the change from baseline (LIN vs. PBO). ANCOVA, analysis of covariance; EQ-5D, EuroQoL-5 dimensions; IBS-QoL, irritable bowel syndrome-quality of life; ITT, intent-to-treat; LIN, linaclotide; LS, least squares; PBO, placebo; VAS, visual analogue scale.

initiating linaclotide therapy, diarrhoea severity was generally mild-to-moderate, and patients appeared to tolerate this adverse effect, as evidenced by the relatively low rate of associated discontinuations (approximately 5%).[25, 26] These findings are consistent with a previous Phase 2b study of linaclotide in patients with IBS-C[24] and two Phase 3 trials in patients with chronic constipation.[30] As previously reported, there were few SAEs and no deaths in either trial.[25, 26]

Although linaclotide significantly improved IBS-C symptoms compared with placebo in both agency-specified analyses, placebo response rates were variable. Response to placebo treatment was higher when assessed using the EMA abdominal pain/discomfort responder endpoint (approximately 40%) than when assessed with either the EMA IBS degree-of-relief responder endpoint (approximately 17%) or the FDA provisional combined abdominal pain and CSBM responder endpoint (13.2–21.0%). High placebo response rates are commonly reported in IBS clinical trials and can limit the probability of demonstrating a beneficial effect of therapy; these rates can be influenced by a number of factors, including diagnostic criteria, duration of therapy and definitions of response.[31] This consistent finding further underlines the importance of trial design and inclusion of multiple recommended endpoints to demonstrate therapeutic efficacy in lieu of an accepted and validated patient-reported outcome.

The FDA and EMA have different requirements for data to support an application for lincensing approval of treatments for IBS-C. This situation poses a significant challenge for sponsors and investigators seeking to design appropriate Phase III clinical trials. Guidance from the FDA recommends that stool frequency is measured as a primary endpoint along with abdominal pain in trials evaluating therapies for IBS.[18] Although assessment of stool frequency may be considered to have the advantage of being a more objective and readily interpretable marker of treatment outcome, the EMA-recommended co-primary endpoints may, arguably, provide a more meaningful evaluation of the impact of treatments on overall IBS symptoms and may be more likely to distinguish therapies effective in IBS-C from those effective in chronic constipation alone. However, the potential shortcomings of overall ratings of change parameters must also be considered, including the challenge for patients of recalling the nature and severity of their symptoms prior to initiating treatment to compare with current symptoms.

Both the EMA and FDA recommend the assessment of abdominal pain as a key efficacy parameter, which reflects the fundamental clinical significance of this symptom in patients with IBS.[32] Patient interviews have shown that abdominal pain, abdominal bloating, constipation and fatigue are perceived to be the most important IBS-C symptoms, whereas other specific constipation-related symptoms, such as straining, incomplete evacuation and hard stool consistency, are felt to be relatively less important.[33] In the present EMA analysis, both abdominal pain and abdominal discomfort were assessed individually as co-primary endpoints. The Rome criteria define discomfort as an uncomfortable sensation that is not described as pain,[4] but there is some doubt as to whether these terms are distinct.[18] Spiegel *et al.* and Fehnel *et al.* found that patients perceive pain and discomfort to be different,

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Table 1 | LS mean changes from baseline to Week 12 in IBS-QoL subscales (ITT population, LOCF)

	Trial 31			Trial 302		
	PBO (n = 395)	LIN 290 μg (n = 405)	LIN–PBO (P)	PBO (n = 403)	LIN 290 μg (n = 401)	LIN–PBO (P)
Dysphoria	17.4	20.4	3.0 (0.02)	13.1	18.4	5.3 (<0.0001)
Interference with activity	13.2	13.8	0.62 (0.61)	9.3	11.6	2.4 (0.04)
Body image	17.9	23.0	5.1 (0.0003)	13.4	21.3	7.9 (<0.0001)
Health worry	19.8	25.2	5.4 (0.0007)	15.8	24.9	9.1 (<0.0001)
Food avoidance	15.9	21.7	5.9 (0.0003)	10.0	18.9	9.0 (<0.0001)
Social reaction	12.4	15.5	3.1 (0.02)	9.5	13.7	4.2 (0.0009)
Sexual	12.6	16.1	3.4 (0.02)	8.8	14.1	5.2 (0.0003)
Relationships	10.2	12.6	2.5 (0.04)	7.3	11.5	4.3 (0.0002)

ANCOVA, analysis of covariance; IBS-QoL, irritable bowel syndrome-quality of life; ITT, intent-to-treat; LIN, linaclotide; LOCF, last observation carried forward; LS, least squares; PBO, placebo.

Data are shown as LS mean change from baseline. *P*-values derived from ANCOVA (LIN vs. PBO).

but their understanding of the distinction between them varies greatly.[33, 34] Although harmonisation of primary endpoint guidance, and development of an accepted and validated patient-reported outcome is warranted, it is likely to remain important for clinical trials to employ multiple endpoints, which assess different aspects of this complex disorder, to support labelling claims.

The issues arising from conflicting guidelines from the FDA and EMA are widely recognised, and as such, the EMA recently announced that they are updating their trial design guidelines for the evaluation of medicines for IBS,[17] which date from 2003. One of the aims of the updated guideline will be to consider existing discrepancies between regulatory authorities, evaluate the possibilities for harmonisation and, potentially, revise the recommendations for the appropriate endpoints for determining the success of an IBS medication. The draft guideline is anticipated in late 2012, and expected to come into effect in 2013.[35]

CONCLUSION

When assessing a complex condition such as IBS, it is important to include multiple efficacy endpoints to ensure that all clinically important symptoms are captured and that the effect of treatment on the patient's full disease experience is measured. To incorporate endpoints recommended by often conflicting guidelines from regulatory bodies in all territories being considered for registration of a new therapy, it is critical at the design stage of a clinical trial to plan outcome measures for all relevant endpoints and to prespecify separate analyses for different registration submissions. Here, we report for the first time, the efficacy of linaclotide in patients with IBS-C, based on efficacy endpoints prespecified for EMA submission. The results of this planned further analysis of two randomised, placebo-controlled Phase 3 trials suggest that once-daily treatment with linaclotide is associated with sustained and significant improvements in both abdominal pain/discomfort and degree-of-relief of overall IBS symptoms over 12 and 26 weeks in patients with IBS-C.

AUTHORSHIP

Guarantor of the article: Prof. E. M. M. Quigley.

Author contributions: Steven J. Shiff, Mark G. Currie and Jeffrey M. Johnston participated in trial design, and data analysis and interpretation. Eamonn M. M. Quigley, William D. Chey, Jan Tack, Satish S. Rao, Josep Fortea, Meritxell Falques and Cristina Diaz participated in data analysis and interpretation. All authors were involved in preparation of the manuscript or revising it critically for important intellectual content, and approved the final version of the manuscript.

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