Safety and patient outcomes with lubiprostone for up to 52 weeks in patients with irritable bowel syndrome with constipation

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SUMMARY

Background
Irritable bowel syndrome with constipation (IBS-C) significantly decreases quality of life and the ability to perform daily living activities.

Aim
To demonstrate the long-term safety, tolerability and patient outcomes of lubiprostone in patients with IBS-C.

Methods
This extension study enrolled 522 IBS-C patients who had completed one of two randomised phase 3 studies. All enrolled patients received open-label lubiprostone orally for 36-weeks (8 mcg, twice daily). The primary objective was the assessment of long-term safety and tolerability, monitored via adverse events (AEs), laboratory parameters and vital signs. Additional outcome endpoints included monthly responder rates and patient evaluations of IBS-C symptom severity and impact on quality of life.

Results
The evaluable safety population comprised of 520 patients; 476 of which had patient reported outcome data available. The overall safety profile of lubiprostone during this study was similar to that observed in the preceding phase 3 studies. The most common AEs were diarrhoea (11.0%), nausea (11.0%), urinary tract infection (9.0%), sinusitis (9.0%) and abdominal distention (5.8%). Diarrhoea and nausea were the most common treatment-related AEs. No serious AEs were considered treatment-related. Seventeen patients discontinued due to a treatment-related AE, of which diarrhoea and nausea accounted for six (1.2%) and three (0.6%) respectively. For responder rates and patient-evaluated parameters ($n = 476$), all groups experienced significant improvements from baseline, with initial improvements maintained throughout the study.

Conclusion
In patients with irritable bowel syndrome with constipation, lubiprostone 8 mcg twice daily was found to be safe and well tolerated over 9–13 months of treatment.

INTRODUCTION

Irritable bowel syndrome (IBS) is defined by the presence of abdominal pain or discomfort that occurs in association with altered bowel habits over a period of at least 3 months.[1, 2] IBS is a common disorder with estimated prevalence rates ranging from 9% to 22% in the USA[3] and accounting for 25–50% of referrals to gastroenterologists.[4] In most parts of the world, IBS occurs more commonly amongst women than men with an estimated prevalence ratio of roughly 2:1.[5]

Individuals with IBS have substantial decrements in their quality of life as well as their ability to perform activities of daily living.[2] Indeed, patients with IBS, compared with those with gastroesophageal reflux disease (GERD), report significantly greater impairments in their ability to carry out daily activity ($P = 0.01$) and work activity ($P < 0.001$), and experience greater work loss ($P = 0.003$).[6] IBS patients who have more severe symptoms also often suffer from coexisting anxiety, depression, somatization disorders or poor coping skills, and commonly have other co-morbid conditions such as fibromyalgia, migraine headaches, interstitial cystitis and temporomandibular joint syndrome.[2] The economic burden of IBS in the USA is estimated to be $20–25 billion annually.[2, 6]

The diagnosis of IBS is commonly based on criteria established by the Rome Committee.[1] IBS is a clinically heterogeneous condition with a broad spectrum of bowel related complaints. The Rome Committee suggests that IBS patients be subgrouped, based upon stool consistency, into those with predominantly constipation (IBS-C), diarrhoea (IBS-D), or a mixture of both (IBS-M). Such subgrouping assists in the appropriate selection of diagnostic testing and treatment.

There are limited treatment options for patients with IBS-C. Although fibre supplements, probiotics and laxatives are commonly utilised, there is little evidence to support their efficacy for the global symptoms of IBS-C.[2]

Lubiprostone, a member of a class of compounds called prostones, is currently an approved therapy in the U.S.A for the treatment of men and women with chronic idiopathic constipation, and women with IBS-C. Data from two randomised, placebo-controlled, multicenter (130 US sites), double-blind phase 3 trials that enrolled patients with IBS-C in accordance with the Rome II criteria, found that lubiprostone 8 mcg administered orally twice daily for 12–16 weeks produced a significantly greater percentage of overall responders compared with placebo (17.9% vs. 10.1%, $P = 0.001$).[7] The current 36-week extension study enrolled eligible patients from these previous two phase 3 trials, and further investigated the long-term safety and tolerability of lubiprostone in the treatment of IBS-C.

METHODS

Study design

This study represents a follow-on open-label, 36-week clinical trial of lubiprostone 8 mcg twice daily to investigate the long-term safety and tolerability of lubiprostone in the treatment of IBS-C. Patients who completed one of two phase 3 studies[8] and were at least 70% compliant with the study medication were eligible to enrol in this extension study. In the first phase 3 study [SIB-0431 (NCT00380250)], patients received treatment with placebo twice daily for 16 weeks or lubiprostone 8 mcg twice daily for 12 weeks, with the latter group then receiving an additional 4-week treatment with either continued lubiprostone or placebo (randomised withdrawal period) (Figure 1a). In the second phase 3 study [SIB-0432 (NCT00399542)], patients were treated for 12 weeks with placebo twice daily or lubiprostone 8 mcg twice daily (Figure 1b). Rollover to the extension study was available to any patient enrolled in the phase 3 studies regardless of response status. However, screening for the extension study was stopped when it was confirmed that least the target of 500 enrolled patients would be met. For illustrative purposes, patients were stratified into one of three enrolment groups based on their treatment allocation in the preceding phase 3 trial, as follows:

(i) Placebo rollover patients: Patients who received placebo in SIB-0431 or SIB-0432 before enrolling in the current extension study (Figure 1a and b). These patients are referred to as placebo/lubiprostone (P/L) patients;

(ii) Lubiprostone/placebo rollover patients: Patients who received lubiprostone during Treatment Period Phase I of SIB-0431 and placebo during Treatment Period Phase II of SIB-0431 before enrolling in the current study (Figure 1a). These patients are referred to as lubiprostone/placebo/lubiprostone (L/P/L) patients; and

(iii) Lubiprostone rollover patients: Patients who received lubiprostone during Treatment Period Phases I and II throughout SIB-0431 or lubiprostone during SIB-0432 before enrolling in the current study (Figure 1a and b). These patients are referred to as lubiprostone/lubiprostone (L/L) patients.

The duration of the active treatment period differed depending on a patient's treatment assignment in the
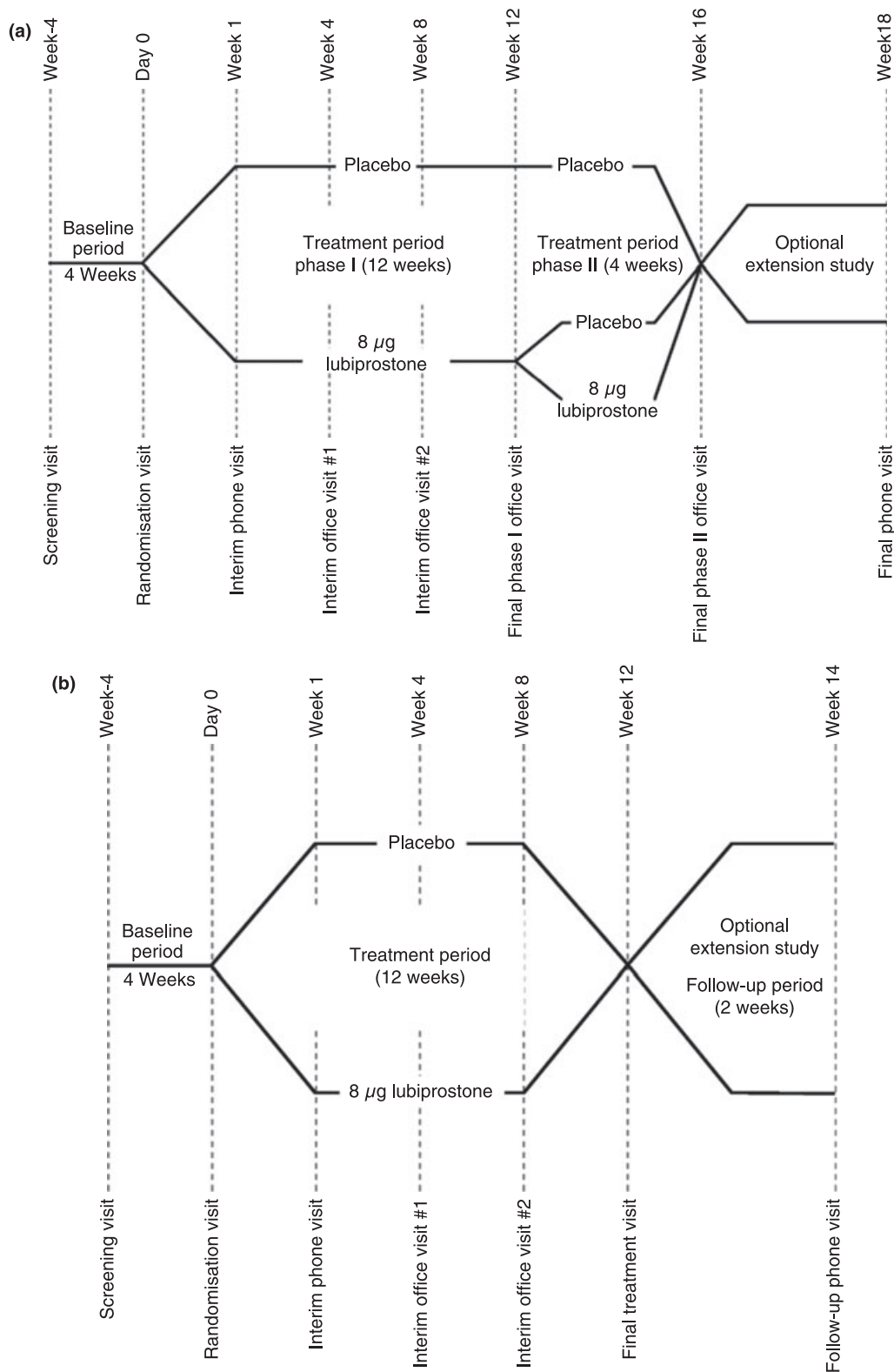
(a)

(b)

Figure 1 | (a) Schematic of study SIB-0431. (b) Schematic of study SIB-0432.

earlier study (Figure 1a and b). As such, if a patient had been in the placebo group (P/L), the patient's data are summarised only from the extension study for a total of 36 weeks of data. If a patient had been in the lubiprostone group (SIB-0432; L/L) or in the lubiprostone/placebo group (SIB-0431; L/P/L), the patient's data from the earlier

study would be combined with the data from this extension study for a total of 48 weeks of data. Finally, if a patient had been in the lubiprostone group (SIB-0431; L/L), data would be combined from both studies for a total of 52 weeks of data.

This current clinical trial was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient prior to undergoing any procedure and the study protocols and any amendments were approved by the institutional review board at each study site.

Open-label treatment and procedures

All patients were treated with lubiprostone 8 mcg administered twice daily. A reduction to once-daily dosing was allowed at the discretion of the investigator if the patient experienced severe nausea or severe diarrhoea for more than two consecutive days, or if the patient experienced some other significant adverse event. Patients returned for office visits at weeks 4, 12, 20, 28 and 36; with telephone follow-up performed at weeks 8, 16, 24, 32 and 2 weeks following the completion of the extension study (week 38).

In the phase 3 studies, as well as during this extension study, patients were instructed to maintain a stable diet that included no significant changes in their consumption of liquids or fibre. They were also instructed not to alter their baseline level of physical activity or to take any new medications for constipation signs and symptoms through the phase 3 or extension study periods. The use of concomitant medications affecting bowel function were not permitted with the exception of 10 mg Dulcolax suppository (bisacodyl, Boehringer Ingelheim GmbH, Ingelheim Rhein, Germany), which was allowed as rescue medication if the patient had not passed a bowel movement for at least 3 days. If bisacodyl was not effective, patients could then administer a Fleet enema (dibasic sodium phosphate and monobasic sodium phosphate; C. B. Fleet, Lynchburg, VA, USA). If both of these options were unsuccessful, an alternative medication could be prescribed at the discretion of the investigator, with the exception of tegaserod maleate. Rescue medications were utilised to affect an immediate bowel movement and not for continuous therapy during the treatment period.

Safety and tolerability assessments

The safety of lubiprostone was assessed by monitoring the incidence, severity and relationship to study medication of all adverse events (AEs) and serious AEs (SAEs). These events included those reported by the patient or by the investigator. The safety of lubiprostone was assessed at each office visit and telephone interview. Patients were prompted to report any changes in their health status while on therapy, including signs and symptoms. AEs were graded by the investigator for intensity and rated as mild (transient symptoms with no interference to daily activities), moderate (marked symptoms with moderate interference to daily activities) or severe (considerable interference to daily activities). The investigator also graded the events for their relationship to study medication as unrelated, unlikely, possible, or probable, and recorded the frequency of the AE as once, intermittent, or continuous.

Tolerability was assessed by the patient's ability to continue treatment without experiencing a treatment-related AE leading to discontinuation or dose reduction of lubiprostone. Patients who discontinued treatment or dose reduced prior to completing the study were considered not to have tolerated lubiprostone.

Blood samples for haematology and biochemistry and urine samples for urinalysis were collected at regular intervals throughout the study period (baseline and weeks 4, 12, 20, 28 and 36). Vital signs, weight, body mass index and physical examinations were also regularly assessed during office visits.

Patient outcome assessments

In the phase 3 and extension studies, the effect of lubiprostone treatment on the symptoms of IBS-C was evaluated on a monthly basis using information from patient diary entries. Data from the baseline period of each initial phase 3 study were used as the baseline for the extension study. Responder status was calculated from the weekly assessments of symptom relief. Symptom relief was assessed in response to the electronic diary question of 'How would you rate your relief of IBS symptoms (abdominal pain/discomfort, bowel habits and other IBS symptoms) over the past week compared to how you felt before you entered the study?' using a 7-point balanced scale (significantly relieved = 1, moderately relieved = 2, a little bit relieved = 3, unchanged = 4, a little bit worse = 5, moderately worse = 6 or significantly worse = 7). A patient was considered a monthly responder if: their symptoms were at least moderately relieved for all 4 weeks within the month, or significantly relieved for at least 2 weeks within the month, and provided that there were no ratings of moderately or severely worse, that the patient did not discontinue treatment during the 4 week period due to a lack of efficacy, and that the per cent of days of rescue medication use did not increase compared with baseline.

Patient evaluations of symptoms of abdominal discomfort/pain, abdominal bloating, SBM and BM frequency rates, stool consistency, bowel straining, constipation severity and symptom relief were also recorded in the diaries. Patients assessed these symptoms (with the exception of stool consistency) using the scale of 0 = absent, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe. Stool consistency was rated as 0 = very loose (watery), 1 = loose, 2 = normal, 3 = hard and 4 = very hard (little balls).

Patients also completed the IBS-Quality-of-Life (IBS-QOL) questionnaire at each office visit.[9, 10] In this validated questionnaire, patients selected 1 of 5 responses to 34 questions regarding the change from baseline in overall quality of life and more specific items in the categories of dysphoria, interference with activity, body image, health worry, food avoidance, social reaction and sexual relationship. Higher scores indicated better quality of life.

Statistical analyses

The sample size in this extension study was determined based on the International Conference on Harmonisation (ICH) guidelines, which state that 300–600 patients treated for 6 months is adequate to characterise the pattern of AEs over time, and that 100 patients treated over 12 months should be sufficient to assess the true cumulative incidence of SAEs and events that increase in severity over time.

Safety analyses were performed using data from all patients who received at least one dose of lubiprostone during the extension study (safety evaluable population). All AEs were coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA; Northrop Grumman Corporation, Chantilly, VA, USA) version 7.0 terminology and AE incidences were summarised by system-organ class and preferred term and by enrolment group. AEs were captured while the patient was receiving study medication or within 7 days of discontinuing study medication. AEs were summarised by the number and per cent of patients who experienced at least one AE, who experienced at least one treatment-related AE, who experienced at least one severe AE, who experienced at least one SAE, who withdrew from the study due to an AE and who died during the study. For clinical laboratory data, descriptive statistics and pre-treatment vs. post-treatment shift tables (with classes for below, within and above normal ranges) were generated.

Patient demographics and baseline characteristics data were summarised by enrolment group with descriptive statistics. Assessment of actual drug exposure was made for each enrolment group. Exposure was based on the number of days of lubiprostone use (first to last dose).

Outcome analyses were determined in the intent-to-treat (ITT) population, defined as all safety evaluable patients who had at least one treatment-period weekly diary entry. For data collected in the diary, the baseline value was the average of the entries from the 28 days before Visit 2 in the preceding study (SIB-0431 or SIB-0432). For nondiary data, the baseline value was the most recently collected value before the first administration of study drug in the preceding study (SIB-0431 or SIB-0432). Responder rates were based on the patient's evaluation of symptom relief and were summarised for all months. The SBM frequency rate was defined as the weekly SBM rate, which was determined from the weekly SBM question. The monthly SBM rate was the average weekly rate over the 4-week period during the month. Values, changes and per cent changes from baseline in constipation symptoms and the IBS-QOL questionnaire at each month were summarised. Mean changes from baseline in IBS-C sign and symptom ratings and the IBS-QOL questionnaire were analysed using the paired t-test if the distribution was found to be normal. Otherwise, the Wilcoxon signed-rank test was used. When presented in figures confidence intervals of 95% were used. At Month 4, the three groups were combined in analyses of responder outcome, as all patients received lubiprostone beyond this point. Multiple imputation was used to assess the effect on response rates for drop-outs that occurred through the follow-up period. The response endpoint is binary, so logistical regression multiple imputation with 25 replications was used. The response rate at each month was then averaged across the 25 datasets providing complete data at each month. Kaplan–Meier product-limit method was used to analyse time to nausea. Repeated time-to-event analysis for repeated nausea episodes was used to examine the effect of duration of lubiprostone exposure.[11] All tests of change from baseline were two-tailed at a significance level of $\alpha = 0.05$ and tested the null hypothesis that the change was equal to zero. Because this is an open-label trial, no inferential analyses comparing enrolment groups were performed.

RESULTS

Patient enrolment and disposition

The first patient was enrolled into the extension study on 26 September 2005 and the last patient completed the study on 20 November 2006. Of the 1171 patients enrolled

into the two phase 3 studies, a total of 522 patients (48.7%) were enrolled into the extension study, of which 520 received open-label lubiprostone and comprised the evaluable safety population (Figure 2). Approximately 66% of the 522 patients ($n = 342$) had received lubiprostone treatment during the previous phase 3 studies (L/L + L/P/L groups); 34% ($n = 180$) comprised the P/L group. Nearly 60% of patients completed the extension study (304/520, 58.2%) with the proportion of completers being greatest in the P/L group (62.8%) and lowest in the L/P/L group (47.5%). A total of 218 patients (41.8%) prematurely discontinued treatment. Lack of efficacy accounted for 18.1% (94 patients) dropping out of the study. Twenty-one (4%) patients discontinued due to AEs. Factors unrelated to treatment were the primary reason for dropping out of the study (103 patients, 19.8%).

Mean overall compliance in the safety evaluable population was 95.3% and differed little among the enrolment groups. Fifteen patients overall (2.9%) were <70% compliant with the dosing regimen. Dose reduction to once-daily dosing occurred in 7.9% of subjects overall (9.7% for the P/L group vs. 7.5% for the L/P/L group vs. 6.9% for the L/L group).

Drug exposure was assessed via the median number of days in the treatment period. Drug exposure was similar among L/P/L and L/L patients (335 and 336 days respectively), and less for the P/L patients, who did not receive lubiprostone until the start of the extension study (252 days).

Patient demographics and disease status characteristics

Patient demographics were similar across the L/L, L/P/L and P/L groups (Table 1), with patients being predominately female (92.9%) and Caucasian (79.8%) with a mean age of 47.2 years (range 21 to 82). Among the 476 patients who comprised the ITT population (patients with at least one diary entry), baseline period disease status (abdominal discomfort/pain, abdominal bloating, constipation severity, weekly SBM frequency, stool consistency, SBM bowel straining and IBS overall QoL) were generally similar across all enrolment groups (Table 2). During the extension study, at least one rescue medication was required by 31.5% of patients (164/520), with the use of rescue medications among the few patients in the P/L arm being lower (9.5%, $n = 17$) than that in either the L/P/L (47.5%, $n = 38$) or L/L arms (41.8%, $n = 109$). The most common rescue medication was Bisacodyl ($n = 155$; 29.8%). Some patients also reported the use of a Fleet ($n = 39$; 7.5%) enema. No other rescue medication was used by more than 2% of the total population.
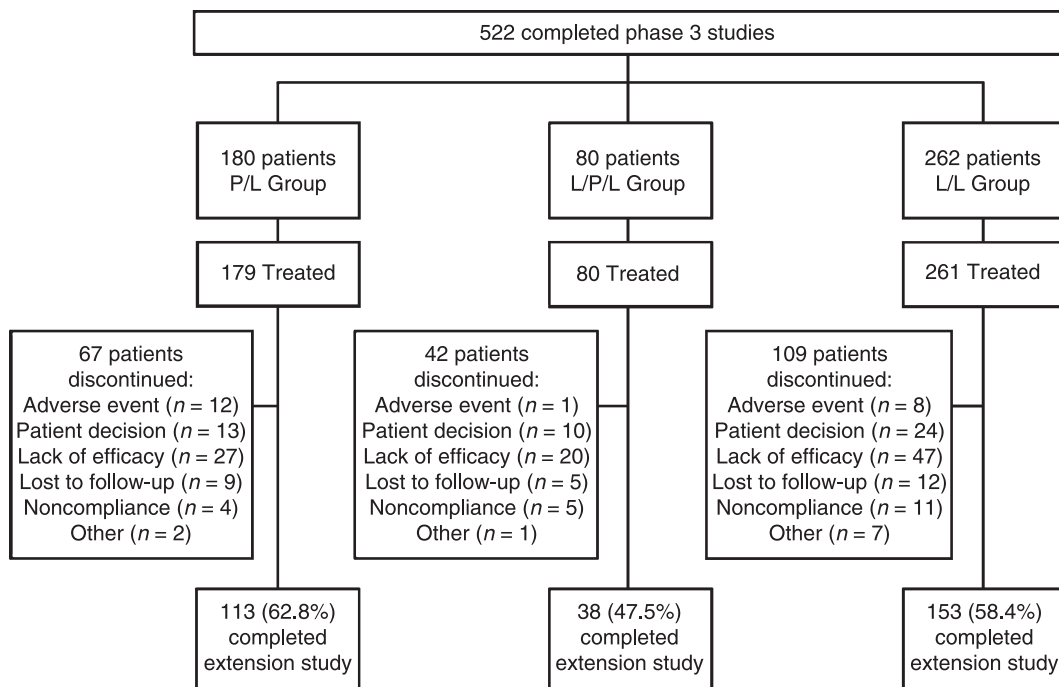

Figure 2 | Patient flow and follow-up during the extension study. Of the 522 patients who enrolled in the open-label extension study, 520 comprised the safety evaluable population and 476 comprised the intent-to-treat population.

Table 1 | Patient demographics by enrolment group

Characteristic	P/L (N = 179)	L/P/L (N = 80)	L/L (N = 261)	Total (N = 520)
Age (years)				
Mean	48.4	46.0	46.7	47.2
s.d.	12.9	10.0	12.5	12.3
Gender, n (%)				
Female	165 (92.2)	78 (97.5)	240 (92.0)	483 (92.9)
Male	14 (7.8)	2 (2.5)	21 (8.0)	37 (7.1)
Race, n (%)				
American Indian/Alaska Native/Asian	1 (0.6)	0 (0.0)	2 (0.8)	3 (0.6)
Black/African American	18 (10.1)	10 (12.5)	31 (11.9)	59 (11.3)
Caucasian	146 (81.6)	60 (75.0)	209 (80.1)	415 (79.8)
Hispanic/Latino	13 (7.3)	10 (12.5)	19 (7.3)	42 (8.1)
Others	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)

Table 2 | Bowel signs and symptoms at baseline in intent-to-treat population

IBS-C sign/symptom	Enrolment group			
	P/L (N = 167)	L/P/L (N = 71)	L/L (N = 238)	Total (N = 476)
Abdominal discomfort/pain	100%	100%	99.6%	99.8%
Discomfort/pain improves after BMs	97.6%	88.7%	93.2%	94.1%
Discomfort/pain associated with BM frequency	85.0%	91.5%	92.8%	89.9%
Discomfort/pain associated with stool consistency	98.8%	98.6%	95.3%	97.0%
<3 BMs per week	92.8%	97.2%	96.6%	95.4%
Hard/Lumpy stools	98.2%	100%	98.3%	98.5%
Straining during BMs	99.4%	100%	98.3%	98.9%
Abdominal discomfort/pain, mean (s.d.)	2.12 (0.64)	2.09 (0.61)	2.09 (0.67)	2.10 (0.65)
Abdominal bloating, mean (s.d.)	2.31 (0.65)	2.31 (0.58)	2.27 (0.68)	2.29 (0.66)
Constipation severity, mean (s.d.)	2.29 (0.64)	2.27 (0.57)	2.22 (0.66)	2.25 (0.64)
Weekly SBM frequency, mean (s.d.)	3.76 (3.44)	3.73 (4.50)	3.86 (3.63)	3.80 (3.70)
SBM stool consistency, mean (s.d.)	2.73 (0.66)	2.78 (0.53)	2.83 (0.68)	2.79 (0.65)
SBM bowel straining, mean (s.d.)	2.39 (0.72)	2.35 (0.78)	2.37 (0.72)	2.38 (0.73)
IBS overall quality of life, mean (s.d.)	55.9 (21.7)	55.6 (22.3)	56.0 (20.9)	55.9 (21.4)

Incidence of adverse events

Overall, 68.7% of patients reported at least one AE and 25.4% reported at least one treatment-related AE (Table 3), with the incidence being similar across the groups.

Among all reported AEs, infection and infestation (36.3%) and gastrointestinal disorders (36.2%) were the most commonly reported system-organ class AEs. As summarised in Table 4, the most common AEs that were reported by at least 5% of patients were diarrhoea (11.0%), nausea (11.0%), urinary tract infection (9.0%), sinusitis (9.0%), abdominal distension (5.8%) and head-ache (5.0%).

Ten patients (1.9%) reported 11 SAEs during the study (three with reproductive system and breast disorders; two each with musculoskeletal & connective tissue disorders and nervous system disorders; and one each with gastrointestinal disorders; injury, poisoning and procedural complications; general disorders; and renal and urinary disorders system categories). None of the 11 SAEs were considered treatment-related and no patients died during the study.

Table 3 | Overall summary of adverse events by enrolment group

	Enrolment group			
Disposition	P/L (N = 179) n (%)	L/P/L (N = 80) n (%)	L/L (N = 261) n (%)	Total (N = 520) n (%)
Patients reporting at least one AE	110 (61.5)	58 (72.5)	189 (72.4)	357 (68.7)
Patients reporting at least one treatment-related AE	44 (24.6)	21 (26.3)	67 (25.7)	132 (25.4)
Patients reporting at least one severe AE	20 (11.2)	9 (11.3)	35 (13.4)	64 (12.3)
Patients reporting at least one serious AE	1 (0.6)	3 (3.8)	6 (2.3)	10 (1.9)
Patients reporting at least one treatment-related serious AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AE, adverse event.

Table 4 | Summary of common treatment-emergent adverse events ($\geq$5% of patients) by body system

	Enrolment group			
Treatment-emergent adverse event	P/L (N = 179)	L/P/L (N = 80)	L/L (N = 261)	Total (N = 520)
Urinary tract infection (%)	11 (6.1)	12 (15.0)	24 (9.2)	47 (9.0)
Sinusitis (%)	15 (8.4)	5 (6.3)	27 (10.3)	47 (9.0)
Nausea (%)	17 (9.5)	5 (6.3)	35 (13.4)	57 (11.0)
Diarrhoea (%)	19 (10.6)	9 (11.3)	29 (11.1)	57 (11.0)
Abdominal distension (%)	9 (5.0)	2 (2.5)	19 (7.3)	30 (5.8)
Headache (%)	7 (3.9)	3 (3.8)	16 (6.1)	26 (5.0)

The most common system-organ class for treatment-related AEs was the gastrointestinal system (21%). Treatment-related AEs that occurred in more than 1% of patients overall included diarrhoea (6.5%), nausea (6.3%), abdominal distension (3.7%), abdominal pain (2.9%), flatulence (2.1%), upper abdominal pain (1.9%), headache (1.5%), dizziness (1.3%) and vomiting (1.2%). Among the 520 enrolled, the number of patients with treatment-related diarrhoea and nausea events reported as severe were 4 (0.8%) and 1 (0.2%) respectively (Table 5).

Of the total 1253 reported AEs, 257 (20.5%) were treatment-related, 45 of which were diarrhoea and 44 nausea. The majority of treatment-related reports of diarrhoea (89%) and nausea (98%) were mild to moderate in severity, and none of the treatment-related reports of diarrhoea and nausea were considered SAEs (Table 6). The incidence rate and severity of diarrhoea and nausea were similar across all groups. In addition, the total number of patient days during the study was 128 052 days. The diarrhoea event rate and treatment-related diarrhoea event rate were 0.60 and 0.35 per 1000 patient days respectively. The nausea event rate and treatment-related nausea event rate were 0.57 and 0.34 per 1000 patient days respectively.

Of the 520 patients enrolled in the study, 21 patients discontinued due to AEs, the most common events were diarrhoea (n = 7; 1.3%), nausea (n = 4; 0.8%), abdomi-

Table 5 | Summary of subjects with diarrhoea and nausea treatment-related adverse events by severity

	Diarrhoea				Nausea			
Severity*	P/L (N = 179)	L/P/L (N = 80)	L/L (N = 261)	Total (N = 520)	P/L (N = 179)	L/P/L (N = 80)	L/L (N = 261)	Total (N = 520)
Mild	3 (1.7)	1 (1.3)	9 (3.4)	13 (2.5)	2 (1.1)	1 (1.3)	12 (4.6)	15 (2.9)
Moderate	8 (4.5)	3 (3.8)	6 (2.3)	17 (3.3)	7 (3.9)	2 (2.5)	8 (3.1)	17 (3.3)
Severe	2 (1.1)	1 (1.3)	1 (0.4)	4 (0.8)	0 (0)	1 (1.3)	0 (0)	1 (0.2)

* If a subject reported more than one nausea/diarrhoea event, the more severe event will be used in the analysis.

Table 6 | Diarrhoea and nausea treatment-related adverse events by seriousness and severity

Description	Diarrhoea				Nausea			
	P/L (N = 15)	L/P/L (N = 6)	L/L (N = 24)	Total (N = 45)	P/L (N = 9)	L/P/L (N = 7)	L/L (N = 28)	Total (N = 44)
Serious AEs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nonserious AEs	15 (100.0)	6 (100.0)	24 (100.0)	45 (100.0)	9 (100.0)	7 (100.0)	28 (100.0)	44 (100.0)
Mild	3 (20.0)	2 (33.3)	12 (50.0)	17 (37.8)	2 (22.2)	2 (28.6)	16 (57.1)	20 (45.5)
Moderate	9 (60.0)	3 (50.0)	11 (45.8)	23 (51.1)	7 (78.8)	4 (57.1)	12 (42.9)	23 (52.3)
Severe	3 (20.0)	1 (16.7)	1 (4.2)	5 (11.1)	0 (0)	1 (14.3)	0 (0)	1 (2.3)

nal distension (n = 3; 0.6%) and dizziness (n = 2; 0.4%). The majority of these AEs were mild and moderate in severity, with severe AEs leading to discontinuation in 3 of the 21 patients. Seventeen of 21 patients discontinued due to a treatment-related AE, of which diarrhoea and nausea accounted for 6 (1.2%) and 3 (0.6%) respectively. Of the 17 patients discontinuing due to treatment related AEs 2 were rated as severe.

Dose reductions occurred in 41 (7.9%) of the 520 patients, four of whom ultimately discontinued. The total number of patients who either discontinued due to a treatment-related AE or dose reduced prior to completing the study was 54 (10.4%). Significant changes from baseline in haematology and biochemical laboratory values, vital signs, weight, BMI and physical examination were not seen over the duration of the study.
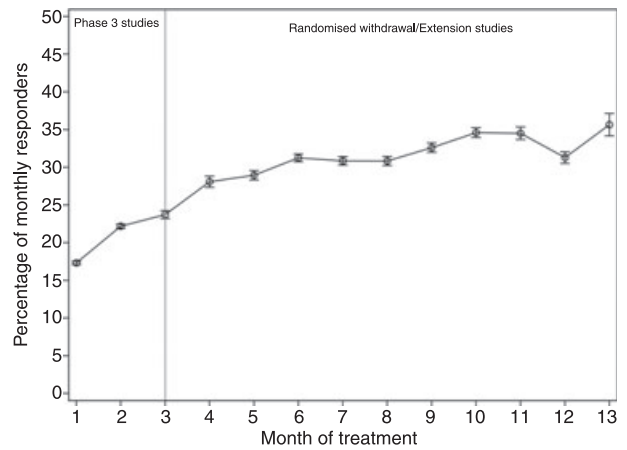

Figure 3 | Monthly responder rates. Early improvement in monthly responder rates were maintained through the extension study even when accounting for drop out.

Patient outcomes

During the phase 3 and open-label extension periods the overall monthly responder rates tended to increase over time with the monthly responder rate at 16% following 1 month of lubiprostone treatment, and subsequently ranged from 23% to 29% following 2–5 months of treatment, 32–35% following 6–9 months of treatment and 37–44% following 10–13 months of lubiprostone treatment. These data do not include patients that dropped out during the extension study. Age, baseline weight and IBS subtype (as classified under Rome III) were predictive of dropout events indicating that younger, lower body weight patients with IBS-D (Rome III) were more likely to dropout. These factors were used in a logistic multiple imputation model to replace missing values. Each missing value was imputed 25 times and the average response frequency was used in the final figure. Figure 3 presents the responder rates with missing data imputed (522 each month through month 9 and 341 for months 10–13). Figure 3 demonstrates that early improvements in monthly response rates are maintained through the extension study even when accounting for dropouts. By month 13

the responder rate is 35% in the imputed data and 44% in the patients with complete data.

As illustrated in Figure 4 (n = 167 P/L; n = 71 L/P/L; n = 238 L/L), mean weekly SBM frequency per month increased following the first month of lubiprostone treatment and remained relatively stable, at approximately five SBMs per week, with continued treatment. Within each group, the change from baseline was significantly different for most months (P ≤ 0.002). Patients' symptoms of abdominal discomfort and pain also improved gradually with open-label lubiprostone treatment, with improvements maintained with continued treatment and ranging from approximately −0.4 after 1 month in each of the three groups and remaining at approximately −0.7 during the remaining course of treatment (Figure 5; n = 167 P/L; n = 71 L/P/L; n = 238 L/L). The improvement in pain scores were significantly different from baseline (P < 0.001) at each monthly assessment, across all groups and throughout the study period.
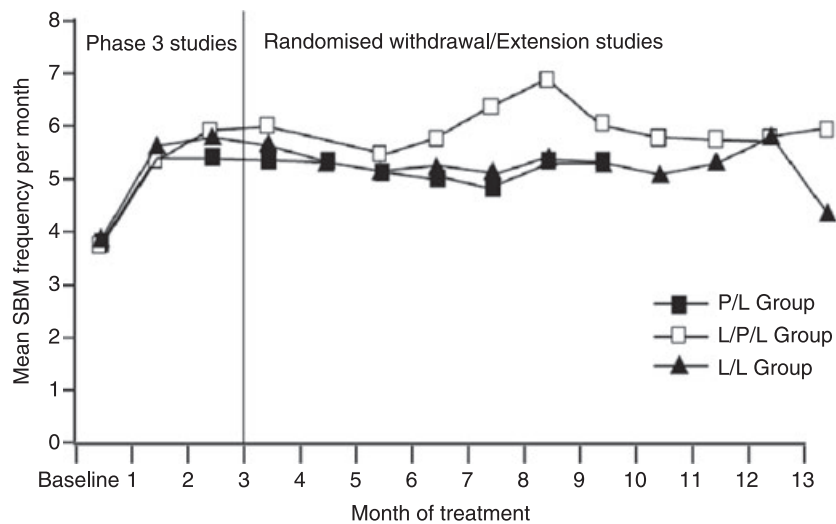
Figure 4 | Summary of SBM frequency per week rates, by group. The mean SBM frequency per week increased during the first month of open-label lubiprostone treatment in all three treatment groups and remained relatively stable thereafter.
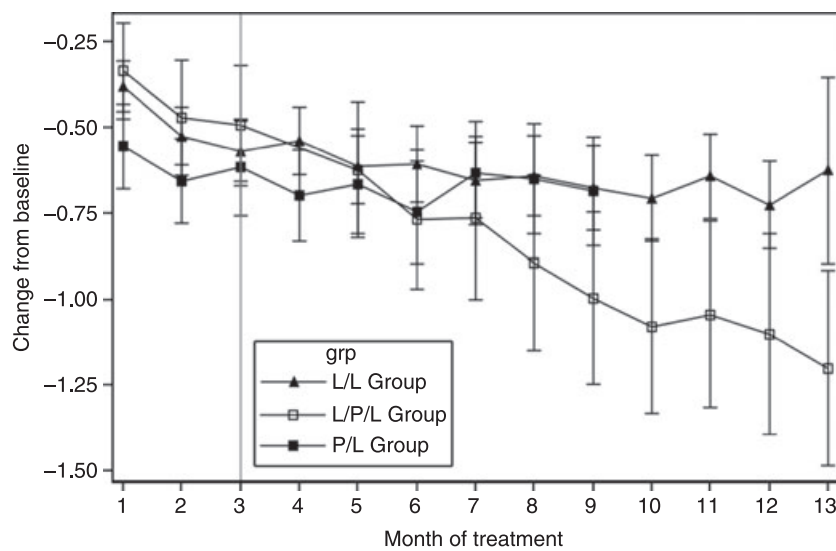

Figure 5 | Abdominal discomfort/pain scores (mean). Using a scale of 0 = absent, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe, there were improvements in patients symptoms of abdominal discomfort/pain during open-label lubiprostone treatment, with improvements maintained during the course of the extension study. 95% confidence intervals for each monthly estimate are provided.

Similar to the ratings of abdominal discomfort/pain, the mean patient ratings for abdominal bloating and stool consistency were significantly improved from baseline in all enrolment groups throughout the study period ($P < 0.001$). The overall improvements in the rating of abdominal bloating ranged from −0.45 at month 1 to −0.87 at month 13, and for stool consistency from −0.50 at month 1 to −0.68 at month 13. Patient scores

for degree of straining demonstrated overall significant improvements ranging from −0.58 at month 1 to −0.81 at month 13; and for constipation severity overall statistically significant improvements ranged from −0.57 at month 1 to −0.87 at month 13.

Using a 7-point balanced scale (significantly relieved, moderately relieved, a little bit relieved, unchanged, a little bit worse, moderately worse, or significantly worse) to
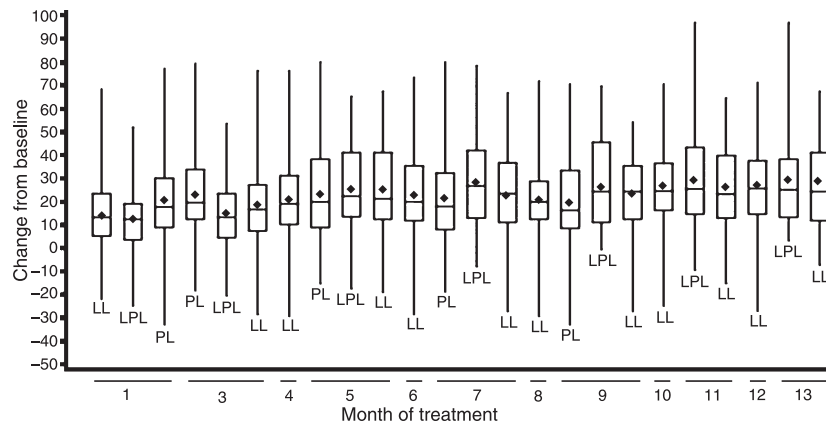
Figure 6 | Monthly change from baseline in overall quality of life by treatment group (ITT patients). At baseline, comparable quality of life scores were reported in each of the three groups (55.9 ± 21.7, P/L; 55.6 ± 22.3, L/P/L, and 55.9 ± 20.9, L/L). All three treatment groups exhibited improvements in their quality of life with continued open-label lubiprostone treatment.

assess symptom relief, the overall change from baseline improvements ranged from 0.96 at month 1 to 1.55 at month 13.

All groups reported similar quality of life scores at baseline (approximately 55.9 in each group). Clinically significant increases in the quality of life scores (indicating improved quality of life over baseline) were observed initially in each treatment group and maintained throughout the study period, with the monthly average change from baseline in treated patients shown in Figure 6.

DISCUSSION

Lubiprostone is a member of the prostone class of compounds. Pharmacologically, it acts on chloride channels (ClC-2) to increase chloride secretion and the passive transport of sodium and water across gastrointestinal mucosal epithelia,[12–14] thereby enhancing transit and ameliorating the symptoms of constipation. Furthermore, recent evidence suggests that some patients with IBS have increased intestinal permeability.[15] Data from recent animal studies suggests that lubiprostone may restore abnormal mucosal barrier function induced by ischaemic injury.[13, 14] Two clinical trials recently assessed the efficacy of lubiprostone for the treatment of IBS-C in adults.[8] The combined results from these two phase 3 trials provide support for the efficacy of lubiprostone in the treatment of the global and individual symptoms experienced by patients with IBS-C. Based upon results from these studies, lubiprostone (8 mcg) was approved by the FDA for the treatment of IBS-C in adult women in April 2008.

The primary objective of this open-label, extension study was to determine the long-term safety of a 16 mcg (8 mcg twice daily) dose of lubiprostone, when administered for 36 weeks in patients with IBS-C who had already received between 12–16 weeks of lubiprostone treatment. Overall, the long-term use of lubiprostone demonstrated a favourable safety profile. The most common AEs reported by >5% of patients were diarrhoea (11.0%), nausea (11.0%), urinary tract infection (9.0%), sinusitis (9.0%) and abdominal distension (5.8%). Approximately 25% of patients in this extension study reported an AE that was thought to be treatment-related. The majority of these treatment-related AEs were mild to moderate in severity, and none were rated to be serious. The most common treatment-related events reported by >1% of patients were diarrhoea, nausea, abdominal distention, abdominal pain, flatulence, abdominal pain upper, headache, dizziness and vomiting affecting between 1% and 6.5% of lubiprostone patients. The majority of events in patients with treatment-related diarrhoea and nausea were mild to moderate in severity with severe treatment-related diarrhoea and nausea reported by 4 (0.8%) and 1 (0.2%) of the 520 patients respectively. It should be noted that the extension study was designed to reflect 'real world' clinical practice, and there was no formal assessment by questionnaire, or otherwise, for specific AEs. As such, the AE data are potentially subject to over- or under-reporting. The incidence and type of treatment-related AEs (approximately 25%) observed in this long-term open-label extension study (36 weeks) were similar to the incidence rate (22%) and type reported for lubiprostone patients in the

earlier two 12 to 16-week phase 3 studies.[8] The 25% incidence of treatment-related AEs observed in this open-label study of 8 mcg lubiprostone was less than the 36% reported in a previous study using 24 mcg twice daily of patients with chronic constipation[16]; similarly, the treatment-related incidence rate for nausea was 6.3% for all patients in this study, compared with nearly 32% in the higher-dose study.[16] These findings suggest a dose response relationship between lubiprostone and the incidence of AEs. It should also be noted that the percentage of patients on placebo reporting an AE and treatment-related AE of nausea in the pivotal phase 3 studies was 5.7% and 3.6% respectively; suggesting that some incidences of nausea reported in this study may be attributable to the patients IBS-C. *Post hoc* analysis revealed that moderate to severe nausea occurred in 3.5% of patients in the current study, with no difference between patients by prior treatment group. Of the 44 treatment-related episodes of nausea reported, the majority of patients (84.4%) had only one episode. Kaplan–Meier analysis, for time to nausea onset, estimates that 67% of nausea episodes occurred within the first week of treatment; a repeated time to event analysis further demonstrated that there was no relationship between time of nausea onset and whether or not the patient had received prior lubiprostone treatment. Ten per cent (n = 54) of patients either discontinued due to a treatment-related AE or dose reduced prior to completing the study, indicating that lubiprostone was well-tolerated with respect to AEs.

Treatment efficacy data from this long-term, open-label study should be interpreted with caution. The absence of a placebo arm, regression to the mean and patient attrition during the study period complicate the interpretation of this data. Multiple imputation was used to address the limitation of attrition in the responder analysis. There was little difference in the monthly responder estimates between the complete cases and imputed analysis through 9 months. After 9 months patients who remained in the study had a substantially higher response than estimated using the imputed data. The data indicates that younger patients, those with lower rate, or components of diarrhoea were more likely to discontinue treatment. Acknowledging these limitations, patients enrolled in this study experienced significant sustained improvements from baseline in their IBS-C associated symptoms including frequency of SBMs, abdominal pain/discomfort, abdominal bloating, stool consistency, bowel straining, constipation severity and symptom relief. Of interest, a *post hoc* analysis revealed that the only patient-reported factor from the week prior to entry into the extension study that was predictive of continued use of lubiprostone and completion of the extension study was symptom relief. Patients who did not complete the extension study reported an average symptom relief score of 0.28 at the end of the phase 3 double-blind period, compared with 0.93 reported by patients going on to complete the long-term study (P = 0.0012). A total of 63–79% of the patients who reported symptom relief at the end of the double-blind period completed the extension study. A similar relationship between symptom relief and completion of the long-term study was also observed at 1 month into the extension study (p ≤ 0.0001). The improvements in IBS-C signs and symptoms are consistent with a recently published phase 2 trial of patients with IBS-C treated with lubiprostone at doses of 8, 16 and 24 mcg, administered twice daily.[17] In this study of 195 patients, significant improvements compared with placebo for abdominal pain/discomfort, abdominal bloating, frequency of SBMs, stool consistency, bowel straining and constipation severity were observed.

As noted earlier, individuals with IBS have substantial decrements in their quality of life as well as their ability to perform activities of daily living. In addition, to the sustained significant improvements in IBS-C symptoms reported with long-term lubiprostone treatment, patients also reported clinically significant improvements from baseline (P ≤ 0.026) in quality of life scores throughout the study period.

In conclusion, the current long-term, open-label extension study demonstrates that lubiprostone, when given for 9–13 months in patients with IBS-C has a favourable safety and tolerability profile and provides preliminary evidence for the efficacy of lubiprostone in the long-term treatment of IBS-C.

ACKNOWLEDGEMENTS

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