Alosetron use in clinical practice: significant improvement in irritable bowel syndrome symptoms evaluated using the US Food and Drug Administration composite endpoint

Brian E. Lacy, Jean Paul Nicandro, Emil Chuang and David L. Earnest

Abstract

Background: Alosetron is approved to treat women with severe IBS and diarrhea (IBS-D) who have failed standard therapy. In our study, we aimed to evaluate alosetron efficacy using new US Food and Drug Administration (FDA) endpoints and utilization in clinical practice.

Methods: This prospective, open-label, multicenter, observational 12-week study evaluated women with severe IBS-D enrolled in the alosetron prescribing program. The coprimary FDA endpoints were changes from baseline in stool consistency and abdominal pain severity. Responders achieved a 30% decrease compared with baseline in weekly average of the worst abdominal pain in the past 24 h, and a 50% or greater reduction from baseline in the number of days/week with at least one stool of type 6 (mushy) or type 7 (watery) consistency. Secondary endpoints included changes from baseline in stool frequency, fecal urgency and fecal incontinence.

Results: Enrolled patients (n = 192) were primarily White (90.6%), with a mean age of 44.5 years. Patient and physician rating of IBS severity was between moderate and severe (85.9% concordance, Spearman coefficient 0.429, p < 0.0001). Alosetron 0.5 mg twice daily (82.8%) was the most common dosing regimen. A total of 152 alosetron-treated patients completed the study. Of 105 fully evaluable patients, 45% met the FDA composite endpoint responder criteria for ≥50% of the study period. Improvements in all individual symptoms were statistically significant compared with baseline. There were no serious adverse events, cases of colonic ischemia, or complications of constipation.

Conclusion: In a clinical practice setting study, alosetron demonstrated treatment success using a rigorous FDA composite endpoint and also improved multiple other IBS symptoms, including fecal urgency and incontinence in women with severe IBS-D [ClinicalTrials.gov identifier: NCT01257477].

Keywords: abdominal pain, diarrhea, fecal incontinence, fecal urgency

Received: 30 October 2017; revised manuscript accepted: 21 March 2018.

Introduction

Large, prospective, multicenter clinical trials are the standard by which the efficacy and safety of a medication are determined in order to obtain regulatory approval. However, due to strict inclusion and exclusion criteria, study populations investigated in pivotal clinical trials are not necessarily representative of the heterogeneous patient population seen by healthcare providers in clinical practice. Therefore, assessments of real-world medication use and treatment outcomes in clinical practice are important.

Alosetron is a selective 5-HT3-receptor antagonist approved by the US Food and Drug Administration (FDA) for the treatment of women with irritable bowel syndrome with...
diarrhea (IBS-D) who have failed conventional therapy. Initially approved in 2000, it was voluntarily removed from the market due to concerns over side effects of constipation and rare events of colonic ischemia.2 The FDA reapproved alosetron in 2002 for the treatment of women with severe IBS-D who had failed to respond to conventional treatment. Two generic formulations of alosetron have recently been approved by the FDA using the same 2002 indication and recommended dosage range.

Interestingly, despite documented efficacy in clinical trials, no prospective studies have been performed in clinical practice settings to evaluate the safety and efficacy of alosetron in women diagnosed with severe IBS-D using Rome III criteria. As well, no studies have evaluated the efficacy of alosetron using the new FDA composite endpoint which requires improvement in both abdominal pain and diarrhea.4

The objectives were to: (a) evaluate alosetron efficacy using the new FDA composite endpoint in women with IBS-D who meet Rome III criteria; (b) evaluate changes in fecal urgency and incontinence during alosetron therapy; (c) measure the clinical utilization pattern of alosetron in real-world clinical-practice settings with respect to patient characteristics, (d) evaluate the dosing regimen prescribed in medical practice (including subsequent adjustments); (e) assess concordance between physician and patient assessments of change in IBS-D symptoms during alosetron treatment, and (f) evaluate drug safety.

Methods
This prospective, open-label, multicenter observational study (Protocol10LOT01 [ClinicalTrials.gov identifier: NCT01257477]) evaluated alosetron use in clinical practice of healthcare providers in the United States enrolled in the Prescribing Program for Lotronex (PPL) in women with severe IBS-D from November 2010 to March 2013.5 Sample size for the study was determined by the number of consenting eligible patients entered during the prespecified 28 months enrollment period. Per PPL guidelines, the recommended starting alosetron dose is 0.5 mg twice daily (b.i.d.) and can be increased to 1 mg b.i.d. after 4 weeks if the starting dose is well tolerated but does not adequately control IBS symptoms. Alosetron should be discontinued in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg b.i.d. Additional dose adjustments were permitted.

A total of 67 investigative sites participated in the study; 31 were gastrointestinal (GI) clinical practice groups, 4 sites were GI academic practices and 32 were primary care sites. Institutional review boards approved the protocol and patients provided written informed consent. Adult females aged 18–65 years diagnosed with IBS-D (according to the Rome III criteria) with IBS symptoms for at least 6 months not adequately controlled by other IBS therapy were enrolled if they met the definition of severe IBS-D by having one or more of the following criteria, as defined in the package insert: frequent and severe abdominal pain/discomfort; frequent bowel urgency or fecal incontinence; or disability or restriction of daily activities due to IBS.1 Three to four patients were entered per investigative site. Exclusion criteria included presence of biochemical or structural abnormalities of the digestive tract, concomitant unstable medical condition(s), history of bloody diarrhea or abdominal pain with rectal bleeding, known or suspected bile acid malabsorption, chronic or severe constipation or complications from constipation, recurrent bowel obstruction, thrombophlebitis or a hypercoagulable state. Patients who were currently constipated or who had no bowel movements for three or more days during the 2-week screening period were excluded.

Data collection
Patients recorded daily diary entries describing bowel habits and IBS pain for 7–14 days during screening. Eligible patients received an alosetron prescription from their healthcare providers and obtained alosetron from a pharmacy. At a baseline visit, patients and healthcare providers completed questionnaires on their perceptions of disease severity, most bothersome symptoms, and satisfaction/success with the prestudy treatment for IBS-D. Patients initiated alosetron treatment after the baseline study visit and completed daily diaries on bowel habit and IBS pain for all 12 weeks of the study. Study visits occurred at 4 and 12 weeks. At the week 12 (exit) visit, patients and healthcare providers again completed symptom and treatment satisfaction questionnaires for comparison with those obtained at baseline.
**Study endpoints**

This study evaluated the composite primary endpoints (abdominal pain intensity and stool consistency) currently recommended by FDA for studies of drugs to treat IBS-D. In addition, as an exploratory endpoint, it also evaluated for overall treatment responder status, as specified in the 2012 ‘Guidance for Industry’ publication. The clinical measurements used to assess for improvement in both abdominal pain intensity and in stool consistency were recorded daily in a diary by the patient during baseline and throughout alosetron treatment. The intensity of the worst abdominal pain occurring in the past 24 h was rated by the patient using a 10-point scale (where 0 = ‘no pain’ and 10 = ‘worst possible pain’). Stool consistency was evaluated for each bowel movement by having the patient visually compare each expelled stool with a standardized scale Bristol Stool Form Scale (BSFS) which presented photographs of seven stool types that varied in consistency from hard balls of stool (type 1) to mushy (type 6) or only liquid stool (type 7). A daily average stool consistency score was calculated if more than one stool was passed each day. Average weekly values for daily abdominal pain intensity scores and for stool consistency scores were calculated and used to evaluate for weekly treatment responder status for these two parameters. A responder for abdominal pain intensity was defined as a patient who experienced a decrease of at least 30% in the weekly average abdominal pain intensity score as compared with baseline. A stool consistency responder was defined as a patient who experienced a 50% or greater reduction in the number of days per week with at least one stool that had a consistency of type 6 or type 7 compared with baseline.

An overall responder to alosetron treatment was defined as a patient who achieved the prespecified improvement in the weekly scores for both abdominal pain intensity and stool consistency for at least 50% of the study weeks, that is, in at least 6 of 12 weeks.

Secondary endpoints included changes from baseline in stool frequency, and proportion of days with fecal urgency and fecal incontinence. Baseline and on-treatment percentage of days with fecal urgency and incontinence were calculated as the total number of reporting days divided by the number of days the patient reported the event, multiplied by 100. The percentage of fecal urgency-free days during alosetron treatment was also calculated for patients who recorded fecal urgency as being present during baseline. The treatment response metric of fecal urgency-free days has been suggested as a useful way to assess treatment response in patients with IBS-D.

Data on the type and number of other IBS therapies used at baseline and during alosetron treatment were collected. The proportion of patients who increased (to 1 mg b.i.d.) or decreased (to 0.5 mg once daily) their dose from the starting dosage regimen of 0.5 mg b.i.d. was analyzed. Dose titrations were based on the investigators’ expertise, with the goal of controlling IBS symptoms.

Patients and physicians rated IBS severity on a scale of 1 (not very severe) to 7 (extremely severe) and identified the symptoms that improved after alosetron treatment. The percentage level of concordance in treatment outcome and improvement in IBS symptoms was compared between patients and their treating physicians. Success and satisfaction with conventional therapy at baseline, or alosetron therapy at week 12 was rated on a scale where 1 = not successful or not satisfied and 7 = extremely successful or extremely satisfied.

**Safety**

All patients who received at least one alosetron dose were evaluated for safety throughout treatment and during follow up. Physical exams, blood counts and serum chemistries were performed at the 4- and 12-week/final visits. Adverse events of ischemic colitis, ischemic changes, ischemia or necrosis of the colon, constipation requiring hospitalization or an emergency room visit, and possible complications of constipation (e.g. obstruction, perforation, intestinal ulceration, toxic megacolon, ileus, or impaction) resulting in hospitalization or emergency room visit were reported within 24 h of discovery by study investigators, regardless of seriousness or severity. Physician impression of alosetron tolerability was rated on a 7-point scale where 1 = not well tolerated and 7 = very well tolerated.

**Statistical analysis**

SAS (Version 9.1, SAS Institute, Cary, NC, US) was used for data analyses.

Baseline average stool consistency score and pain severity scores were calculated for the screening period and weekly during alosetron treatment. Week 4 and 12/study termination results and
Therapeutic Advances in Gastroenterology

4 journals.sagepub.com/home/tag

changes from baseline were tested by nonparametric Wilcoxon rank-sum test, and summarized descriptively.

Concordance between patient and physician assessments of overall success of treatment outcome, as well as improvement in individual symptoms from baseline to the week 12 evaluation was also undertaken. Evidence for concordance (lack of significant difference) in the patient versus physician assessment was assessed using McNemar’s test.

Results

Study population and baseline characteristics
A total of 256 patients were screened and 192 (75%) enrolled (Figure 1). Reasons for screen failure \( (n = 64; 25\%) \) included: screening criteria not being met (17.2%), consent withheld or withdrawn (31.3%), or the patient was unable to pay the cost of the study medication (21.9%). Other reasons for screen failure and disposition of the randomized patients are shown in Figure 1. A total of 192 patients were started on study medication (see Figure 1). Forty of these patients discontinued the study medication. The main reasons for discontinuation were inadequate relief of symptoms \( (n = 11) \), adverse events \( (n = 10; 7 \) with worsening abdominal pain; 2 with increased constipation, and 1 with worsening diarrhea) or lost to follow up \( (n = 6) \). A sum of 152 patients completed the study. Fully evaluable data sets were incomplete in 47 of these patients, due to the provider not completing all forms or the patient not answering all questions on the questionnaires at each visit. Thus, the fully evaluable (per protocol) patient population consisted of 105 patients for whom all study visits and procedures per protocol were completed.

Patient characteristics and baseline IBS symptoms are shown in Table 1. Most patients were White (90.6%); the mean age was 44.5 years. Patients’ mean abdominal pain score was 4.2, while stool consistency was loose, with a mean BSFS of 5.2. Fecal urgency occurred on >75% of baseline days and fecal incontinence occurred on approximately 18% of these days (see Table 2).

Results of patient and healthcare provider assessments of overall IBS severity at baseline are shown in Table 1. Both groups assessed IBS severity as between moderately severe and severe, with an 85.9% concordance (Spearman coefficient 0.429, \( p < 0.0001 \)). The percentage of patients meeting each of the criteria for severe IBS-D, as specified in current alosetron labeling, was 92% for frequent and severe abdominal pain and discomfort; 98% for frequent bowel urgency or fecal incontinence; and 88% for disability or restrictions of daily activities due to IBS. The majority of patients (84.4%) met all three severity criteria, while 15.6% met two of three criteria.

Alosetron dosing and dosing adjustments. Baseline alosetron dosing regimens and adjustments during the study were determined from the physicians’ prescribing information. The most common starting alosetron regimen was 0.5 mg b.i.d. (159/192, 82.8%) followed by 0.5 mg once daily (22/192,
11.5%), 1 mg b.i.d. (4/192, 2.1%), and other doses (7/192, 3.6%). The 0.5 mg b.i.d. regimen was also the most common at 4 and 12 weeks (55.6% and 54.6% of patients, respectively). During the study period, 54% of patients remained on the baseline dose without any changes, while 16% had their dose titrated upwards, and 22% had their dose titrated downwards. A total of 25% patients had multiple dose adjustments.

### Efficacy analyses

**Composite endpoint of irritable bowel syndrome pain and stool consistency.** The FDA composite endpoint was determined from patient-reported changes in both IBS pain and in stool consistency. The proportion of both enrolled (intent-to-treat population) and evaluable patients meeting responder criteria for the composite endpoint during each of the 12 weeks of the study is shown in Figure 2(a) and was similar in each population. By week 3, 43% of evaluable patients met the criteria and this response was largely sustained for the rest of the 12-week study. A total of 45% of evaluable patients were considered to be overall responders, since they met the FDA composite endpoint criteria for ≥50% of the 12-week study period.

**Freedom from fecal urgency (100% improvement).** The percentage of patients with fecal
urgency at baseline, and who were urgency free at each study week, is shown in Figure 2(b).
Only five patients (4.7%) of the evaluable population (n = 105) reported no fecal urgency during baseline. By 4 weeks of alosetron treatment, 26% of those who had baseline fecal urgency (n = 100) reported being urgency free (p < 0.0001). During week 8, the number of patients free of fecal urgency had increased to almost 31% (p < .0001) and by the end of the study, 39.6% of patients did not report urgency (p < 0.0001). Responders were those patients who became completely free of fecal urgency for at least 50% or at least 75% of days during study treatment. The 50% responder value was 69% [95% confidence interval (CI) = 59.0, 77.9] and the 75% responder value was 47% (95% CI = 36.9, 57.2).

**Individual bowel symptoms.** Improvements in individual IBS-D bowel symptoms during baseline and alosetron treatment, as well as the calculated change from baseline at weeks 4 and 12, are shown as mean values [± standard error of the mean (SE)] in Table 2. All changes from baseline at 4 and 12 weeks were statistically significant. A total of 44% (45/105) and 65% (64/105) of evaluable patients achieved at least a 30% decrease in abdominal pain at weeks 4 and 12, respectively. Stool consistency improved by at least one point for 55% (55/105) of patients at week 4 and 64% (65/105) at week 12 (p < 0.001). The number of stools/day, the percentage of days with urgency, and percentage of days with fecal incontinence were also significantly reduced from baseline at weeks 4 and 12. The percentage of days with fecal incontinence and fecal urgency by study week are shown in Figure 3. Alosetron significantly reduced fecal incontinence (p = 0.003 at week 3; p < 0.0001 for weeks 4–5 and 7–10; <0.003 for week 11; and p < 0.0005 for week 12). Fecal urgency improved at all specified evaluation points during the 12-week study (please see below, p < 0.0001).

**Patient and physician assessments of improvement in symptoms and overall treatment success.** Patient and healthcare provider perceptions of alosetron’s impact on individual IBS symptoms after 12 weeks for the evaluable population (n = 105) correlated well. More than two thirds of patients reported improvements in abdominal pain/discomfort, urgency, diarrhea, and interference of IBS-D symptoms with daily activities. Similarly, healthcare providers documented improvements in the same symptoms for two thirds or more of the patients. With the exception of control of urgency (p = 0.03), assessments for symptom improvement were not statistically different between the patients and their physicians. Improvement in

Table 2. GI symptoms after 4 and 12 weeks of alosetron treatment (Fully Evaluable Population, n = 105).

| Endpoint                      | Baseline mean ± SE | Week 4 mean ± SE | Week 4 mean change from baseline ± SE | Week 12 mean ± SE | Week 12 mean change from baseline ± SE |
|-------------------------------|--------------------|------------------|---------------------------------------|------------------|----------------------------------------|
| IBS pain severity*            | 4.40 ± 0.23        | 3.36 ± 0.23      | −1.04 ± 0.16 <0.0001                   | 2.45 ± 0.23      | −1.94 ± 0.19 <0.0001                   |
| Stool consistency**           | 5.22 ± 0.12        | 3.95 ± 0.13      | −1.27 ± 0.11 <0.0001                   | 3.76 ± 0.14      | −1.45 ± 0.13 <0.0001                   |
| Stool frequency (#/day)       | 3.75 ± 0.25        | 2.79 ± 0.21      | −0.91 ± 0.16 <0.0001                   | 2.64 ± 0.19      | −1.05 ± 0.19 <0.0001                   |
| % days w/fecal urgency        | 79.29 ± 2.62       | 46.15 ± 3.08     | −31.59 ± 3.17 <0.0001                  | 34.46 ± 3.22     | −42.78 ± 3.45 <0.0001                  |
| % days w/fecal incontinence   | 17.64 ± 2.58       | 12.57 ± 1.96     | −5.07 ± 2.1 <0.0001                    | 8.67 ± 1.79      | −7.62 ± 2.1 <0.0001                    |

Week 4 and 12 values were calculated using data collected in the 28 days prior to the week 4 and 12 study visits.

*11-point pain severity scale where 0 = no pain and 10 = worst possible pain.
**Bristol Stool Form Scale: 1 = hard and 7 = watery.
IBS, irritable bowel syndrome; SE, standard error of the mean; w, with.
Figure 2. Efficacy of alosetron in women with severe irritable-bowel-syndrome-associated diarrhea.

(a) Percentage of patients who were responders for the FDA composite IBS pain and stool consistency endpoint each week of the study. Responders were patients having a 30% decrease in the weekly average of the worst abdominal pain in the past 24 h and a decrease of at least 50% in the number of days per week with at least one stool that had a consistency of type 6 or 7 (Bristol Stool Scale) compared with baseline.

(b) Percentage of patients free of fecal urgency each week of the study. The percentage of patients in the evaluable population reporting fecal urgency at baseline (n = 100) who were urgency free for each week of the study. The percentage of patients that were urgency free for either 50% or 75% of days during treatment is shown in the inset. p values are based on McNemar’s test for patients with nonmissing values.

FDA, US Food and Drug Administration; IBS, irritable bowel syndrome.

Symptoms of bloating was somewhat less than for the other symptoms noted above, being reported by 35% of patients and more than 40% of physicians (difference not statistically significant).

Assessments of overall treatment success with alosetron made independently by the patients and their healthcare providers demonstrated means of 5.6 ± 0.13 and 5.7 ± 0.14, respectively, on the
7-point scale (1 = not successful; 7 = extremely successful). Concordance between patient and physician assessment of alosetron success was 90.5% (Spearman coefficient 0.758, p < 0.001).

Concomitant irritable bowel syndrome medications. IBS-related medications were used by 51/192 patients (26.6%) during the 30 days prior to enrollment in the study and had to be taken at a stable dose to be eligible for the study. Patient satisfaction with medications used during baseline to treat IBS symptoms was 2.4 ± 0.12 (out of seven points maximum). During baseline (7–14 days), the only ‘IBS medication’ used by more than 5% of patients was loperamide hydrochloride (n = 13, 6.8%). During the 12-week study, 96 patients (50%) used IBS-related concomitant medications. The most frequent concomitant medications were loperamide hydrochloride, diphenoxylate-atropine and hyoscyamine sulfate which were used by 29 (15.1%), 17 (8.9%) and 14 (7.3%) of patients, respectively. The mean number of IBS-related medications used during the study (0.7 ± 1.0) was similar to the mean number used at baseline (0.8 ± 1.1).

Safety and tolerability
Healthcare provider impression of tolerability was 6.2 ± 0.10 (out of seven points) for the evaluable population. Treatment-emergent adverse events (TEAEs) occurred in 44.3% of enrolled patients (85/192) and 22.9% (44/192) had a drug-related adverse event. The most common TEAE (>5 patients) are shown in Table 3, and included constipation (23/192, 12%), abdominal pain (18/192, 9.4%), and nausea (9/192, 4.7%). There were no serious adverse events. More specifically, there were no cases of colonic ischemia, no reports of complications of constipation, and no deaths during the study. Thirteen patients (6.8%) stopped treatment due to one or more adverse events.

Discussion
This study enrolled women with severe IBS-D, as defined by the current product label for alosetron. All patients were derived from the clinical practices of healthcare providers enrolled in the PPL. Although patients needed to meet only one criterion in the label to initiate alosetron, the vast majority of patients in the study (84%) met all three symptom-severity criteria, and both patients and healthcare providers concurred on the overall IBS severity at baseline. Thus, patients in this study are typical of those currently treated in ‘real world’ clinical practice.

Alosetron has been previously studied in a large number of single- and repeat-dose studies. This prospective observational trial is unique in that it is the first alosetron study to enroll patients using the Rome III criteria. In addition, it is the only prospective study of alosetron in which treatment efficacy was evaluated by the new FDA composite endpoint, the current benchmark for demonstrating
efficacy in pivotal regulatory trials. The overall treatment responder rate, using this rigorous FDA requirement, was 44.6%, demonstrating alosetron’s high level of control of abdominal pain and diarrhea, the two cardinal symptoms of IBS-D evaluated by the FDA composite endpoint. Importantly, one of the most bothersome symptoms of IBS-D, fecal urgency, also significantly improved during this study. Calculation of responder status for freedom from fecal urgency during treatment showed that the 50% and 75% responder rates during alosetron treatment were 69% and 47%, respectively. These responder rates during alosetron treatment compare favorably with those observed during eluxadoline (100 mg b.i.d. dose) treatment (41% and 23%, respectively), a mixed μ-opioid receptor agonist/δ-opioid receptor antagonist approved by the FDA in 2015 for IBS-D. Evaluation of responder status for complete relief of fecal urgency during treatment with rifaximin, another drug approved by FDA for IBS-D treatment in 2015, has not been fully reported. A review of alosetron, eluxadoline, and rifaximin efficacy and safety demonstrated that alosetron had the greatest numerical treatment response using the FDA composite endpoint.11

Alosetron efficacy was consistent with that reported in previous clinical trials that used higher initial starting doses of alosetron.12–16 Importantly, this prospective study is the only trial which evaluated IBS-D patients with the currently recommended starting dose of 0.5 mg of alosetron b.i.d. with clinical monitoring to assess the need for dosing changes as indicated by treatment response. A previous randomized, controlled study in women with severe IBS-D (Rome II criteria) demonstrated that alosetron doses of 0.5 mg once daily, 1 mg once daily, and 1 mg b.i.d. were all effective in providing global improvement in IBS symptoms, adequate relief of IBS pain and discomfort, and improvement in bowel symptoms.17 The lower starting doses also resulted in statistically significant and clinically relevant improvements in health-related quality of life, restriction of daily activities, and treatment satisfaction compared with placebo.18 However, there was no opportunity to change the dose if treatment response was inadequate. In our real-world clinical-practice management study, no dosing adjustments were required for the majority of patients whose treatment was initiated at the recommended starting dose of 0.5 mg b.i.d., indicating that IBS symptoms are well controlled in the majority of patients at the recommended lower alosetron starting dose.

There was excellent agreement between patient and healthcare provider perceptions of IBS severity at baseline and symptom improvement during alosetron treatment. This concordance is improved over that reported in previous studies comparing patient and healthcare provider perceptions of IBS symptoms and severity19 and may reflect the success of the alosetron risk management program in selecting appropriate patients for treatment, as well

| Table 3. The most commonly reported* treatment-emergent adverse events for all enrolled patients, and relationship to study drug. |
|-----------------|-----------------|-----------------|
|                  | Patients (%)    | Drug-related TEAE patients (%) |
|                  | n = 192         |                               |
| **At least one TEAE** |                 |                               |
| Constipation     | 23 (12.0)       | 22 (11.5)                  |
| Abdominal pain   | 18 (9.4)        | 10 (5.2)                   |
| Nausea           | 9 (4.7)         | 5 (2.6)                    |
| Diarrhea         | 6 (3.1)         | 3 (1.6)                    |
| Headache         | 5 (2.6)         | 0                           |
| Anxiety          | 6 (3.1)         | 0                           |
| **Serious TEAE** | 0               | 0                           |

This table includes all patients who received at least one dose of alosetron. *Occurring with a frequency of greater than or equal to 5%. TEAE, treatment-emergent adverse event.
as the greater understanding of severe IBS-D among physicians enrolled in the PPL.

Alosetron was well tolerated during the current study and there were no cases of ischemic colitis or complications of constipation. These results reinforce the recommended dosing regimen and support the conclusion that the PPL successfully mitigates the occurrence of alosetron-related severe adverse events.20,21

Limitations of the study include that it was non-blinded and no control group was used. Cost of the medication also limited approximately 6% of patients from participating, which is common in medical practice. Had the currently lower-priced generic version of alosetron been available at the time of the study, it might have allowed more patients to participate. Similar to nearly all IBS studies, the enrolled population was predominantly White. Unfortunately, there is a paucity of data regarding alosetron treatment outcomes in other races or ethnic groups. Although no cases of ischemic colitis occurred during this study, the sample size was not adequately powered to identify this, given that the risk of ischemic colitis in alosetron users is calculated at approximately 1 in 1000 users.20,21 Finally, this study allowed patients to continue to use other available medications taken during baseline for IBS-D symptoms, as long as the dose remained stable. However, this does not diminish the positive findings reported in the study, since patients entered the study only because they were symptomatic despite current treatment.

**Conclusion**

In this real-world clinical-practice assessment of alosetron use in women with severe IBS-D who met current labeling prescribing requirements, dosing with alosetron was consistent with labeling guidelines and there were minimal dose adjustments during the 3 months of treatment. Alosetron significantly improved multiple IBS symptoms, including IBS pain and stool consistency using the FDA composite endpoint, fecal urgency, and incontinence. Patients and healthcare providers had similar assessments of the improvement in multiple IBS symptoms during alosetron treatment. Alosetron was well tolerated and there were no reports of colonic ischemia or complications of constipation during the 3 months of observation. Overall, these results support use of alosetron as a clinically effective treatment for severe IBS-D in women who have not responded adequately to other treatments.

**Acknowledgements**

We thank the study site investigators, personnel, and patients for their participation in the study. Patrice C Ferriola, PhD, provided assistance in writing the article and was funded by Prometheus Laboratories.

Brian E Lacy, PhD, MD, helped design the study, participated in the clinical trial, and contributed materially to the development of the manuscript. Jean Paul Nicandro, PharmD, Emil Chuang, MD, and David L Earnest, MD, assisted with the conduct of the study (JPN and EC), contributed materially to study analysis, and participated in the development of the manuscript. All authors approved the final version of the article.

**Funding**

Prometheus Laboratories provided support in full for the conduct of the study and for manuscript preparation. Writing support was provided by Patrice C Ferriola of KZE PharmAssociates, LLC, and was funded by Prometheus Laboratories.

**Conflict of interest statement**

JP Nicandro and E Chuang were employees of Prometheus Laboratories at the time of the study. DL Earnest is Emeritus Professor of Medicine (Gastroenterology) at The University of Arizona College of Medicine in Tucson, AZ, and was a consultant for Prometheus Laboratories Inc. at the time of the study.

BE Lacy is Senior Associate Consultant, Division of Gastroenterology and Hepatology, at Mayo Clinic, Jacksonville. In the last 5 years, he has served as an advisory board member to Ironwood, Allergan, Salix, and Prometheus.

**References**

1. LOTRONEX. Lotronex prescribing information, San Diego, CA: Prometheus Laboratories, Inc, http://www.lotronexppl.com/ (2014, accessed 13 January 2017).

2. Miller DP, Alfredson T, Cook SF, *et al*. Incidence of colonic ischemia, hospitalized complications of constipation, and bowel surgery in relation to use of alosetron hydrochloride. *Am J Gastroenterol* 2003; 98: 1117–1122.
3. Cremonini F, Delgado-Aros S and Camilleri M. Efficacy of alosetron in irritable bowel syndrome: a meta-analysis of randomized controlled trials. Neurogastroenterol Motil 2003; 15: 79–86.

4. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for industry: irritable bowel syndrome—clinical evaluation of drugs for treatment, http://www.fda.gov/downloads/Drugs/Guidances/UCM205269.pdf (2012, accessed 14 July 2012).

5. Miller D, Bennett L, Hollis K, et al. A patient follow-up survey programme for alosetron: assessing compliance to and effectiveness of the risk management programme. Aliment Pharmacol Therapeut 2006; 24: 869–878.

6. Longstreth GF, Thompson AR, Chey WD, et al. Functional bowel disorders. In: Drossman DA, Corazziari E, Delvaux M, et al. (eds). Rome III: the functional gastrointestinal disorders. 3rd ed. McLean, VA: Degnon Associates, Inc., 2006, pp. 487–555.

7. Lembo A, Andrae D, Dove S, et al. Urgency as a measure of treatment effect due to eluxadoline. Am J Gastroenterol 2014; 109(Suppl. 2): S542.

8. Lehmann E. Nonparametrics: statistical methods based on ranks. San Fransisco: Holden-Day, 1975, p. 562.

9. Ford AC, Brandt LJ, Young C, et al. Efficacy of 5-HT3 antagonists and 5-HT4 agonists in irritable bowel syndrome: systematic review and meta-analysis. Am J Gastroenterol 2009; 104: 1831–1843.

10. Lembo A, Dove S, Andrae D, et al. Eluxadoline for the treatment of diarrhea-predominant irritable bowel syndrome: results of 2 randomized, double-blind, placebo-controlled phase 3 clinical trials of efficacy and safety. Gastroenterology 2014; 146(Suppl.1): S159.

11. Cash BD, Lacy BE, Rao T, et al. Rifaximin and eluxadoline - newly approved treatments for diarrhea-predominant irritable bowel syndrome: what is their role in clinical practice alongside alosetron? Expert Opin Pharmacother 2016; 17: 311–322.

12. Camilleri M, Northcutt AR, Kong S, et al. Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomised, placebo-controlled trial. Lancet 2000; 355: 1035–1040.

13. Camilleri M, Chey W, Mayer E, et al. A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant IBS. Archives Int Med 2001; 161: 1733–1740.

14. Lembo T, Wright RA, Bagby B, et al. Alosetron controls bowel urgency and provides global symptom improvement in women with diarrhea-predominant irritable bowel syndrome. Am J Gastroenterol 2001; 96: 2662–2670.

15. Chey WD, Chey WY, Heath AT, et al. Long-term safety and efficacy of alosetron in women with severe diarrhea-predominant irritable bowel syndrome. Am J Gastroenterol 2004; 99: 2195–2203.

16. Lembo AJ, Olden KW, Ameen VZ, et al. Effect of alosetron on bowel urgency and global symptoms in women with severe, diarrhea-predominant irritable bowel syndrome: analysis of two controlled trials. Clin Gastroenterol Hepatol 2004; 2: 675–682.

17. Krause R, Ameen V, Gordon SH, et al. A randomized, double-blind, placebo-controlled study to assess efficacy and safety of 0.5 mg and 1 mg alosetron in women with severe diarrhea-predominant IBS. Am J Gastroenterol 2007; 102: 1709–1719.

18. Cremonini F, Nicandro JP, Atkinson V, et al. Randomised clinical trial: alosetron improves quality of life and reduces restriction of daily activities in women with severe diarrhoea-predominant IBS. Aliment Pharmacol Ther 2012; 36: 437–448.

19. Casiday RE, Hungin AP, Cornford CS, et al. GPs' explanatory models for irritable bowel syndrome: a mismatch with patient models? Fam Pract 2009; 26: 34–39.

20. Chang L, Tong K and Ameen V. Ischemic colitis and complications of constipation associated with the use of alosetron under a risk management plan: clinical characteristics, outcomes, and incidences. Am J Gastroenterol 2010; 105: 866–875.

21. Tong K, Nicandro JP, Shringarpure R, et al. A 9-year evaluation of temporal trends in alosetron postmarketing safety under the risk management program. Therap Adv Gastroenterol 2013; 6: 344–357.