

# Clinical Roundtable Monograph

Gastroenterology & Hepatology

November 2013

## An Evidence-Based Look at Misconceptions in the Treatment of Patients with IBS-D

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### Abstract

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal disorder and affects up to 12% to 15% of adults in the United States, with a higher prevalence among women and those younger than 50 years. IBS adversely impacts quality of life and medical expenditures, with significant costs arising from healthcare visits and reduced workplace productivity. Recent studies have shown that the adverse effects of IBS are so significant that many patients are willing to accept risks of adverse events from effective treatment to gain symptom relief. Alosetron is a 5-HT<sub>3</sub> receptor antagonist approved by the US Food and Drug Administration (FDA) for women with severe diarrhea-predominant IBS that has not responded to traditional therapies. Alosetron yields overall improvements in IBS symptoms in 51% of patients vs 36% treated with placebo, with efficacy continuing undiminished over the course of a 48-week randomized, controlled trial. In real-world clinical practice, patients receiving alosetron had significant improvements in multiple IBS-related clinical parameters, including the new FDA IBS-diarrhea composite endpoint, lower gastrointestinal symptoms, fecal incontinence, and quality of life. Ischemic colitis and complications of constipation have been rare in occurrence. After nearly a decade of alosetron use under the risk management plan, adjudication of ischemic colitis and complications of constipation cases indicate that their incidence rates have remained low and stable.

## Table of Contents

Risk Tolerance in the Management of IBS	
Brian E. Lacy, MD, PhD	3
Efficacy of Alosetron in the Management of IBS-D	
William D. Chey, MD	8
Reassessing Alosetron Risk-Benefit Based on the Latest Postmarketing Safety Data	
Lin Chang, MD	12
Discussion	
Brian E. Lacy, MD, PhD, William D. Chey, MD, and Lin Chang, MD	17
Conclusion	
Brian E. Lacy, MD, PhD	20

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# Risk Tolerance in the Management of IBS

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## Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal (GI) disorder encountered by all healthcare providers, irrespective of specialty or training. Functional GI disorders are defined by symptoms and by the absence of findings by chemical, radiologic, and/or endoscopic tests that seek to identify an organic cause for patient symptoms. Clinically, IBS is characterized by the presence of abdominal pain or discomfort that is temporarily improved or relieved by defecation. Use of the Rome III criteria,<sup>1</sup> along with a careful history and physical examination, allows IBS to be confidently diagnosed and appropriately subtyped by the predominant stool pattern (Table 1). The stool symptoms include constipation, meaning IBS with constipation (IBS-C); diarrhea (IBS-D); or mixed constipation and diarrhea (IBS-M).

IBS is one of the most frequent diagnoses encountered in gastroenterology practices. It accounts for 25% to 50% of gastroenterology referral visits.<sup>2</sup> IBS affects approximately 7% to 10% of persons globally, and up to 12% to 15% of adults in the United States. The prevalence of IBS is higher among women and among those younger than 50 years.<sup>3</sup>

IBS impacts quality of life and economics,<sup>4,5</sup> and it impacts both patients and the healthcare community at large. Patients with IBS have worse health-related quality of life than healthy controls, and their health-related quality of life is comparable to that of patients with diabetes, gastroesophageal reflux disease, depression, and end-stage renal disease.<sup>6,7</sup> For example, many patients with IBS-D commonly forgo social activities with family or friends because they fear that they may not be close enough to a bathroom or that they may have an episode of incontinence.

IBS also has a socioeconomic impact. In the United States, approximately 3.5 million healthcare visits occur each year for IBS.<sup>8</sup> The direct and indirect costs of IBS were estimated at more than \$20 billion annually in the year 2000.<sup>9</sup> Healthcare costs are significantly higher for patients with IBS than for age- and sex-matched controls, with estimates for these higher healthcare costs rang-

**Table 1.** Diagnosis of IBS: Rome III Criteria

Symptom onset at least 6 months prior to diagnosis
Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with 2 or more of the following: <ul style="list-style-type: none"> <li>• Improvement with defecation</li> <li>• Onset associated with a change in stool frequency</li> <li>• Onset associated with a change in stool form (appearance)</li> </ul>
One or more of the following symptoms on at least a quarter of occasions for subgroup identification <ul style="list-style-type: none"> <li>• Abnormal stool frequency (&lt;3/week)</li> <li>• Abnormal stool form (watery or lumpy/hard)</li> <li>• Abnormal stool passage (straining, incomplete evacuation)</li> <li>• Bloating or feeling of abdominal distension</li> <li>• Passage of mucus</li> <li>• Frequent, loose stools</li> </ul>

IBS, irritable bowel syndrome.

Data from Longstreth GF et al. *Gastroenterology*. 2006;130(5):1480-1491.<sup>1</sup>

ing from \$5000 to \$11,000 per patient.<sup>10</sup> The greater indirect costs associated with IBS are in part due to higher absenteeism among persons with IBS compared to those without IBS, and also due to lost productivity in the workplace, which is known as *presenteeism*.<sup>11</sup> Presenteeism has been estimated to cause the loss of up to 14 hours of a 40-hour work week among patients with moderate to severe IBS.<sup>11</sup>

The mechanisms proposed as a cause for IBS are complex, and its exact pathophysiology remains unclear. IBS is more prevalent in women, and differences in sex hormones or sex-related responses to stress and inflammation may play contributory roles (although only weak evidence supports this hypothesis).<sup>12</sup> Genetic factors also appear to play a role in the development of IBS, since monozygotic twins have higher concordance rates of IBS than dizygotic twins, who in turn have higher prevalence rates than the general population.<sup>13</sup>

Dysfunction in the brain-gut axis in IBS may be associated with abnormalities in perception and/or modulation of visceral input. This results in abnormal levels of abdominal pain, which may be due to both visceral and

**Table 2.** Risk Tolerance of IBS Patients to Achieve Symptom Relief if Treated with a New Medication

	Death		Serious or Permanent Adverse Events		Mild Adverse Events	
	All (N=1966)	Severe IBS (N=400)	All (N=1966)	Severe IBS (N=400)	All (N=1966)	Severe IBS (N=400)
<b>Acceptable Patient Risk for Total IBS Symptom Relief:</b>	%	%	%	%	%	%
Would Not Take	30.2	21.3	39.6	32.8	8.8	5
1/10 million	15.4	13.5	16.3	14	7.3	9
1/1 million	17.6	15.8	17.2	15.3	7.3	4
1/100,000	14.5	14.5	9.9	12	9.5	6.3
1 in 10,000	8.9	10.3	6.9	7.3	11.9	10.8
1 in 1,000	5.8	10	4.5	7.5	14.5	13.8
1 in 100	4.2	6.3	2.6	4.3	14.3	14.5
1 in 10	1.5	3	1.3	3	9.1	11
1 in 5	0.9	2	0.7	1.5	4.2	4.8
1 in 3	0.2	0.3	0.2	0.5	1.9	2
1 in 2	1.1	3.3	0.8	2	11.3	19

IBS, irritable bowel syndrome.

Adapted from Drossman DA et al. *J Clin Gastroenterol.* 2009;43(6):541-550.<sup>22</sup>

central processes. Immune dysregulation has been implicated in IBS as a result of mucosal biopsies that found increased expression of T cells, mast cells, and cytokines in these patients.<sup>14,15</sup> Some patients in whom IBS develops, particularly those patients in whom symptoms occur after an episode of bacterial enteritis, may have an inflammatory component in the underlying mechanism.<sup>16</sup> Other putative causes of IBS include alterations in cytokine levels, overgrowth of bacteria in the small intestine, and chronic dysbiosis.<sup>17-19</sup>

To establish the diagnosis of IBS by the Rome III criteria, which are the most recent iteration of the Rome diagnostic criteria, the patient must have recurrent abdominal pain or discomfort for at least 3 days per month in the last 3 months with symptom onset at least 6 months before diagnosis and the presence of at least 2 of the following: symptoms improve with defecation, onset is associated with change in stool frequency, and onset is associated with change in stool appearance.<sup>1</sup> The use of the Bristol stool scale may help some patients better describe stool consistency and allow physicians to better categorize these patients. Additional symptoms that are common to patients with IBS include bothersome bowel gas, bloating, distention, passing mucus in stool, and straining at stool or feelings of incomplete evacuation.

Patients commonly ask, "What's my prognosis?" First, recognize that the diagnosis of IBS tends to remain

stable over time. A literature review of 14 longitudinal studies found that an alternative organic disorder was diagnosed in only 2% to 5% of clinic-based patients with IBS who were followed up for periods that ranged from 6 months to 6 years.<sup>20</sup> When the natural history of IBS was followed over a 10-year period, 67% of the patients had persistent IBS symptoms at 10 years.<sup>21</sup>

Another question that arises is the stability of the IBS subtype. Although the diagnosis of IBS generally remains stable, symptoms may fluctuate over time. Many patients with IBS-D or IBS-C may shift subtypes to an IBS-M pattern.

## Risk Tolerance

A new area of research in gastroenterology is the identification and evaluation of risk-taking behavior in patients. It is important because patients behave differently when confronted with the risks of different types of medications. Recent studies clearly show that IBS patients, particularly those with more severe symptoms, want relief and are willing to trade some risk from the treatment for a greater degree of symptom relief (Table 2).<sup>22-24</sup>

The concept of patient willingness to take risks with prescribed therapy in order to gain relief from a disorder was first explored in patients with another very bothersome condition, Crohn's disease. Johnson and colleagues

**Table 3.** Treatment Options for IBS-D

	Improvements in Symptoms					Grade*	FDA-Approved for IBS-D?
	Global Symptoms	Pain	Bloating	Stool Frequency	Stool Consistency		
<b>Alosetron</b>	+	+	+	+		1B	Yes
<b>Antibiotics (rifaximin)</b>	+		+			1B	No
<b>Antidepressants</b>	+	+				1B	No
<b>Loperamide</b>				+	+	2C	No
<b>Antispasmodics</b>	±	+				2C	No
<b>Probiotics (<i>Bifidobacterial</i> some combinations)</b>	+					2C	No

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

\*Recommendations are based on the balance of benefits, risks, burdens, and sometimes cost: Grade 1, strong; Grade 2, weak. Assessment of quality of evidence is according to the quality of study design, consistency of results among studies, directness, and applicability of study endpoints: Grade A, high; Grade B, moderate; grade C, low.

Adapted from ACG Task Force on IBS. *Am J Gastroenterol.* 2009;104(suppl 1):S1-S35.<sup>40</sup>

surveyed gastroenterologists and patients with Crohn's disease to determine how assessment of treatment benefits and risks influence decisions. Their findings were based on responses from 315 gastroenterologists and 580 patients.<sup>23</sup> Patients were willing to accept a 5.86% risk that they would develop an infection in 10 years for improvement from moderate symptoms to remission. They were also willing to accept a 1.52% risk of developing progressive multifocal leukoencephalopathy in 10 years for improvement from severe to moderate symptoms. Physicians were willing to accept a 3.14% risk of infection in 10 years for improvement from moderate symptoms to remission. They were also willing to accept a 4.24% risk of developing progressive multifocal leukoencephalopathy for improvement from severe to moderate symptoms.<sup>23</sup>

Our laboratory recently published a study that investigated the willingness of patients with IBS to take risks with a hypothetical medication that could cure their symptoms.<sup>24</sup> The study involved 186 patients with IBS that met Rome III criteria. These patients had a mean age of 48 years, and approximately 85% were women. These patients had long-standing IBS, with a mean symptom duration of 13.6 years. They represented a mixture of IBS subtypes, with 45% meeting the criteria for IBS-D, 16% for IBS-C, and 38% for IBS-M.

Anxiety and depression were measured with the Hospital Anxiety and Depression Scale. Overall, these patients had higher anxiety and depression subscores compared with healthy controls and the general population, an observation documented in other studies of patients with IBS.<sup>25-27</sup>

The most interesting finding was that patients with IBS were more willing to take significant medication risks to improve their symptoms. Overall, these patients were

willing to accept a 1% risk of sudden death if offered a 99% chance of cure for their IBS using a hypothetical medication. The severity of IBS symptoms corresponded to an increased tolerance for risk. Age, sex, and years of IBS symptoms did not affect medication risk-taking behavior. Importantly, patients with IBS and diarrhea who had used alosetron reported that they were willing to accept an even higher risk (median 2.5% chance) of sudden death if a hypothetical medication could cure their IBS symptoms.

## Management of Patients with Irritable Bowel Syndrome

There are many approaches to management of IBS. Fiber appears to offer some benefit. A recent meta-analysis showed it was more effective than placebo in the treatment of IBS.<sup>28</sup> Calcium channel blockers may also offer improvement in IBS symptoms.<sup>29</sup> Over the past several decades, conventional pharmacotherapy for IBS-D has been largely focused on individual symptom relief, rather than addressing the underlying cause of IBS. Conventional agents include antidiarrheal agents, such as loperamide or diphenoxylate-atropine, and smooth muscle antispasmodics, such as hyoscyamine or dicyclomine (Table 3). These typically target only 1 symptom. Although commonly prescribed, the safety and efficacy of these agents in IBS-D have not been established in large, randomized, placebo-controlled trials or remain under clinical investigation. We will focus on alosetron, which has the highest degree of evidence for effective treatment and remains the only agent approved by the US Food and Drug Administration (FDA) for the treatment of appropriate patients with IBS-D.

## Background on Alosetron

Alosetron, a selective serotonin 5-HT<sub>3</sub> receptor antagonist, is approved by the FDA for the treatment of women with severe IBS-D who have had an inadequate response to conventional IBS pharmacotherapy. In clinical studies, alosetron has demonstrated significant efficacy for IBS. It has improved fecal urgency, stool frequency, and stool consistency.<sup>30,31</sup> In women with severe IBS-D, alosetron has improved global symptoms of IBS and provided adequate relief of associated pain and discomfort.<sup>32-34</sup> Based on clinical trial data, alosetron initially gained approval in the United States in 2000.

## Use Under the RMP/REMS

Nine months after its approval, alosetron was voluntarily withdrawn by GlaxoSmithKline based on postmarketing reports of rare but confirmed cases of ischemic colitis and complications of constipation. In November 2002, requests from IBS patients and patient advocacy groups led to the reintroduction of alosetron under a risk management plan (RMP),<sup>35</sup> which was converted to a risk evaluation and mitigation strategy (REMS) in 2010. Alosetron is currently available to patients under this program, which ensures patient knowledge about how to maximize safe use of the drug.

Clinical trials of alosetron found that constipation was the most common adverse event associated with its use. Constipation is estimated to occur in approximately 24% of women with IBS-D treated with alosetron compared with approximately 6% treated with placebo in clinical trials.<sup>36</sup> Constipation appears to be a dose-related effect. Many in clinical practice would question whether this adverse event is of concern, since our IBS-D patients come to the clinic with persistent symptoms of diarrhea and fecal urgency that have failed standard therapy, including loperamide and diphenoxylate-atropine. Nonetheless, the FDA requires constipation to be reported as an adverse event. In the vast majority of patients, constipation is mild and transient, generally resolving with dose reduction or cessation of the medication.

The 2 most serious adverse events associated with the use of alosetron are ischemic colitis and complications of constipation. Although ischemic colitis is frequently discussed, recent evidence shows that in reality it occurs at a low rate of approximately 1.03 cases per 1000 patient-years.<sup>37</sup> It appears to be an idiosyncratic event, and it is not dose-related. The rate of serious complications of constipation has declined over time and is estimated at 0.25 cases per 1000 patient years.<sup>38</sup> Serious complications of constipation include impaction, ileus, bowel obstruction, and, rarely, toxic megacolon. Under the alosetron RMP

and subsequent REMS, there have been no transfusions or deaths in adjudicated cases of ischemic colitis; and no deaths, surgeries, toxic megacolon, or intestinal perforations in adjudicated cases of complications of constipation.

The alosetron RMP and subsequent REMS program have been remarkably successful. Postmarketing surveillance demonstrated that the incidence of ischemic colitis and complications of constipation have remained rare and stable over time, and that serious outcomes have been mitigated over nearly a decade under the RMP/REMS program.

## Summary of Alosetron Clinical Studies

Eight large, well-designed, randomized clinical trials involving 4170 patients show that alosetron significantly improves multiple symptoms of IBS-D, such as abdominal pain, urgency of global IBS symptoms, and diarrhea-related complaints compared with placebo.<sup>36</sup> The studies that assessed changes in stool frequency and consistency showed significant improvements with alosetron vs placebo.

In a recent real-world study of alosetron, the FDA-recommended composite endpoint of demonstrating IBS-D efficacy in abdominal pain and stool consistency was met by over 45% of patients treated with alosetron.<sup>39</sup> The results of these well-controlled studies show that alosetron addresses 2 broad categories of medical needs in patients with IBS and diarrhea. It improves individual symptoms, such as abdominal pain, stool frequency, stool consistency, urgency, and episodes of incontinence. It also improves global symptoms, which encompass the individual symptoms as well as areas that are more difficult to measure, such as quality of life, economics, and patients' well-being.

In the next 2 sections of this monograph, William D. Chey, MD, will discuss efficacy of alosetron in the management of IBS-D, and Lin Chang, MD, will provide an updated risk-benefit analysis of alosetron based on the latest postmarketing safety data. We will then engage in a roundtable discussion of timely, clinically relevant issues in the management of IBS-D. I will close with some concluding remarks.

## Acknowledgment

*Dr Lacy is a co-investigator for the NIH Functional Dyspepsia Treatment Trial. In the last 2 years, he has served on the scientific advisory boards of Ironwood, Takeda, and Prometheus.*

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# Efficacy of Alosetron in the Management of IBS-D

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## Impact of Alosetron on Clinical Outcome

Alosetron is a 5-HT<sub>3</sub> receptor antagonist that targets a specific set of serotonin receptors that play an important role in GI motility, transit, and sensation. This agent offers important benefits for the management of IBS-D symptoms, as demonstrated in a recent systematic review and meta-analysis.<sup>1</sup> More recent studies include an alosetron vs conventional therapy study<sup>2</sup> and alosetron efficacy in real-world, clinical practice.<sup>3</sup> The systematic review and meta-analysis included 11 randomized, controlled trials in over 7200 patients with IBS. Among these, 8 of the randomized trials were conducted with alosetron (the remaining 3 were with cilansetron), of which a total of 5 alosetron studies were in female patients with IBS. All of the trials had Jadad scores of at least 4, suggesting moderate to high methodologic quality.<sup>4</sup>

The meta-analysis demonstrated that treatment with alosetron, compared with placebo, resulted in statistically and clinically significant improvement in global IBS symptoms or abdominal pain, as reflected in an overall relative risk of symptom persistence of 0.79 (95% CI, 0.69-0.90; Figure 1). The number needed to treat with alosetron was 8 (95% CI, 5-17). This level of improvement is high amongst the hierarchy of therapies for IBS.

Significant heterogeneity existed among the trials, with variations in inclusion criteria, patient populations, drugs, and doses within a specific drug category. There was no statistical evidence of publication bias.

The 8 trials that examined alosetron had a very consistent message. All but 1 showed significant benefits for alosetron compared with placebo. The overall odds of benefit in the alosetron trials appeared very similar to the overall results yielded by the analysis that included all 11 trials of the various 5-HT<sub>3</sub> receptor antagonists.

## Effects in Female IBS-D Patients

A 12-week randomized, double-blind, placebo-controlled trial that included 705 women was the first to fully evaluate the effects of alosetron in female patients with severe

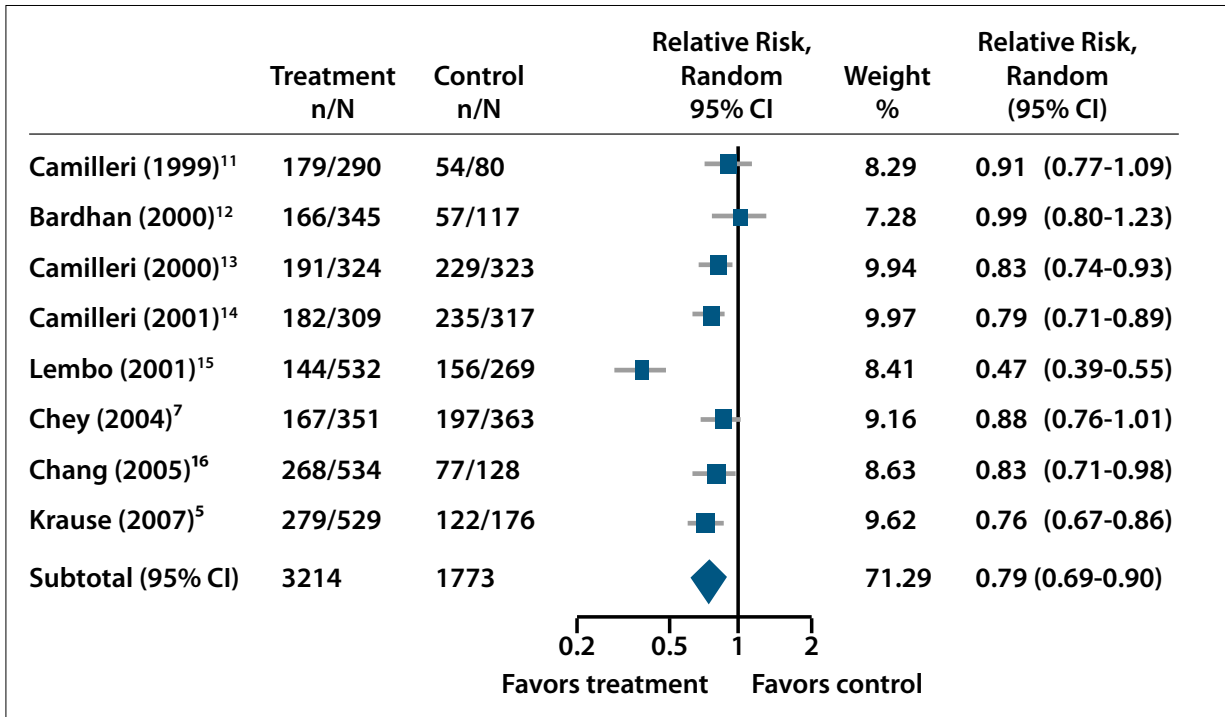
IBS-D.<sup>5</sup> This study was also one of the first randomized controlled trials to investigate a lower dose of alosetron. It compared 3 doses (0.5 mg daily, 1 mg daily, or 1 mg twice daily) against placebo. All 3 doses of alosetron provided statistically significant benefits vs placebo for overall improvement of global IBS symptoms. Additionally, a number of individual IBS-related symptoms, including urgency, stool frequency, and stool consistency, significantly improved with alosetron compared with placebo.

Additional results of this trial examined the effects of alosetron on health outcomes, specifically IBS-related quality of life, restriction in daily activities, and treatment satisfaction.<sup>6</sup> Treatment with alosetron led to significant improvements in IBS-related quality of life, restriction in daily activities, and treatment satisfaction over placebo. Importantly, IBS symptom improvement corresponded with positive changes in quality of life, workplace productivity, and treatment satisfaction. This study was one of the first to show that alosetron improved not only symptoms but also that the improvement correlated with positive changes in health outcomes in women with severe IBS-D.

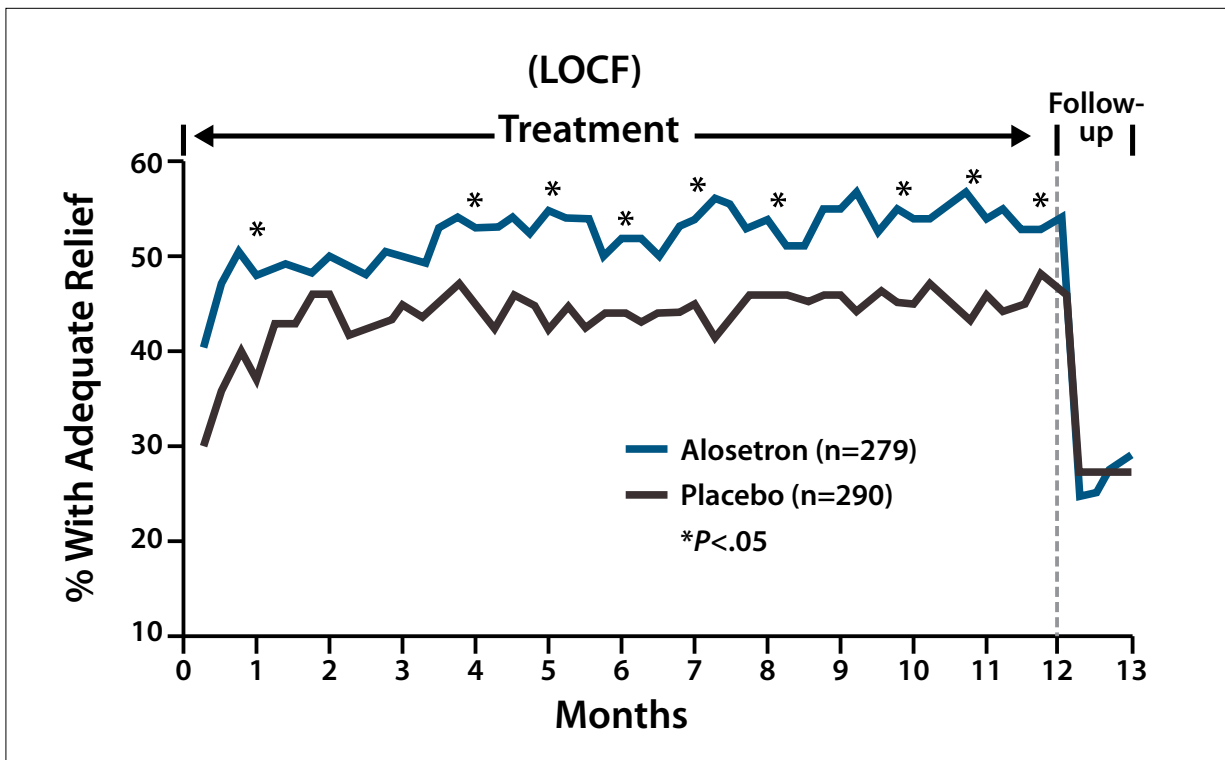
## Long-Term Efficacy

Most of the randomized controlled trials in IBS have been of short duration, typically utilizing a treatment period of 12 weeks. The efficacy of few agents has been rigorously evaluated for longer periods. A long-term, randomized controlled trial investigated the efficacy and safety of alosetron for 48 weeks.<sup>7</sup> During this trial, the statistically significant effects of alosetron observed over the first 3 months proved durable for the entire 48-week randomization period (Figure 2). Alosetron was associated with significantly greater rates of adequate relief of pain/discomfort ( $P=.01$ ) and urgency control ( $P<.001$ ) throughout most of the 48 weeks compared with placebo. This improvement was seen regardless of rescue medication use. Patients with more frequent urgency had more robust responses than other patients ( $P=.005$ ). In weeks during which patients did not use rescue medication, satisfactory control rates for stool frequency and stool

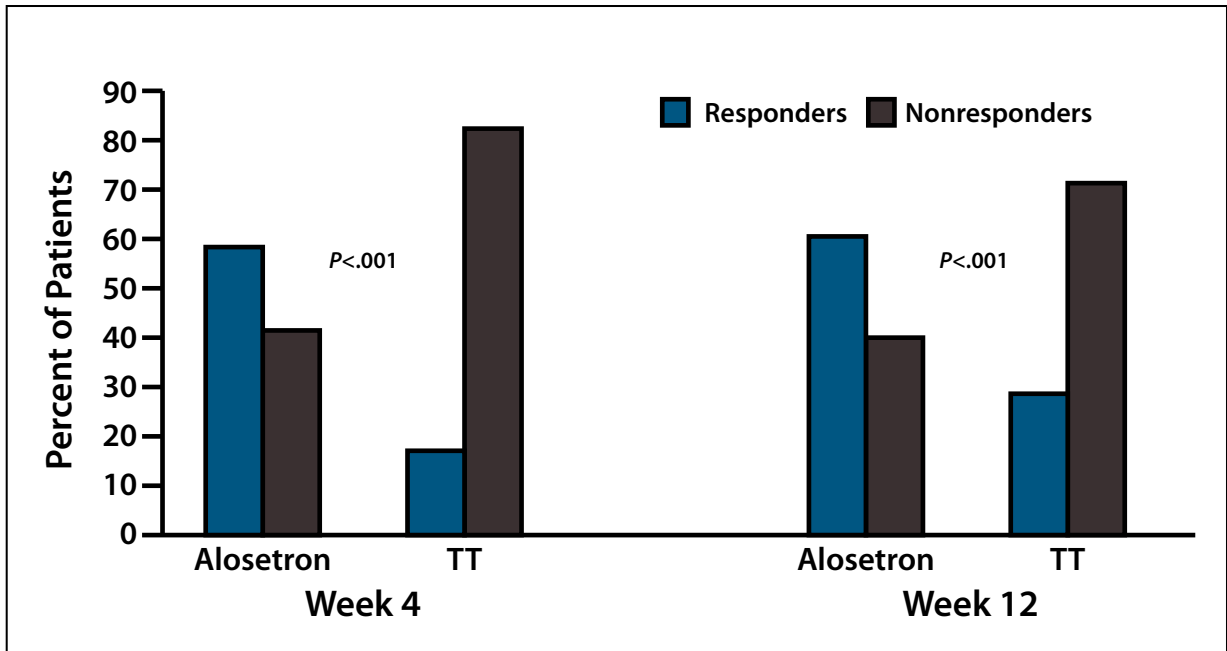




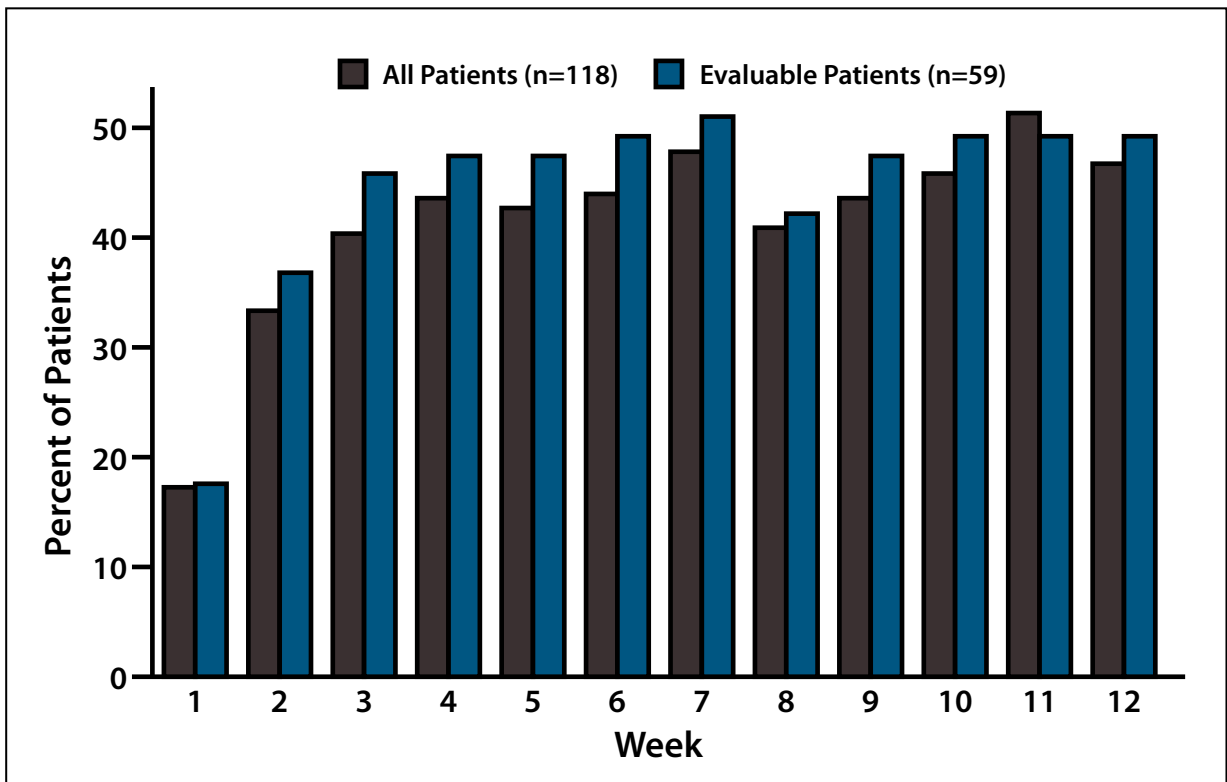
**Figure 1.** Forest plot for alosetron studies in irritable bowel syndrome. A Forest plot depicts the relative strength of treatment effects in multiple quantitative scientific studies addressing a certain question.<sup>17</sup> Adapted from Ford AC et al. *Am J Gastroenterol.* 2009;1049(7):1831-1843.<sup>1</sup>



**Figure 2.** Long-term efficacy of alosetron for diarrhea-predominant irritable bowel syndrome. LOCF, last observation carried forward. Adapted from Chey WD et al. *Am J Gastroenterol.* 2004;99(121):2195-2203.<sup>7</sup>



**Figure 3.** A significantly greater proportion of alosetron patients achieved moderate or substantial improvement (responders) according to the Global Improvement Scale as compared with the traditional treatment (TT) arm. Adapted from Chey WD et al. DDW abstract Tu1386. *Gastroenterology*. 2013;76(6).<sup>2</sup>



**Figure 4.** The proportions of all patients and evaluable patients satisfying the FDA irritable bowel syndrome-diarrhea composite endpoint for diarrhea-predominant irritable bowel syndrome reflecting treatment success. The composite endpoint was defined as demonstration of efficacy on at least 50% of weeks in the study.<sup>9</sup> FDA, US Food and Drug Administration; IBS-D, Adapted from Lacy BE et al. DDW abstract Tu1393. *Gastroenterology*. 2013;76(6).<sup>3</sup>

consistency were significantly higher with alosetron than placebo. As compared with the placebo arm, patients who received alosetron experienced significantly greater adequate relief in 9 of 12 months ( $P < .05$ ) and significantly greater urgency control in all months ( $P < .001$ ). Throughout treatment, alosetron maintained adequate relief and urgency control. Importantly, the safety profile also remained stable. Constipation was more common in the alosetron arm, but other adverse events and serious adverse events were similar between the treatment groups. There were no reports of ischemic colitis or serious events related to bowel motor dysfunction.

## Efficacy from Recent Studies

### *Alosetron vs Traditional IBS Therapy*

The efficacy and safety of alosetron compared with conventional therapies for IBS was evaluated in a 24-week, open-label clinical trial.<sup>2</sup> Women with severe IBS-D were randomized 2:1 to either open-label alosetron or traditional therapy (eg, anticholinergics/antispasmodics, antidepressants, nonsteroidal anti-inflammatory drugs, antidiarrheals, proton pump inhibitors, laxatives) for up to 24 weeks. The trial studied more than 1900 women: 1346 were randomized to alosetron, and 625 received traditional therapy. The patients who were treated with alosetron reported significantly fewer office and clinic visits for any health problem, as well as for IBS. Alosetron-treated patients also used significantly fewer over-the-counter medications for IBS, had fewer days of lost work productivity, and reported less restriction of outdoor activities compared with patients who received traditional therapy. Consistent with previous results, alosetron improved quality of life scores for all 9 domains of the Irritable Bowel Syndrome Quality of Life Questionnaire (IBS-QOL). Global IBS symptoms improved in a significantly greater proportion of patients treated with alosetron than in those on conventional therapies (Figure 3). In this large trial of women with severe IBS-D, alosetron therapy reduced healthcare utilization and improved symptoms more effectively than conventional IBS-D therapy.

### *Alosetron Use in Clinical Practice*

Another recent trial investigated the effectiveness of alosetron in real-world clinical practice using the FDA-recommended IBS-D composite endpoint.<sup>3,8</sup> This trial enrolled 134 women with IBS-D, with 81% receiving alosetron 0.5 mg twice daily, 12% receiving 0.5 mg once daily, and the rest receiving some combination of 1-mg dosing. The patients received alosetron for 12 weeks. By week 3, more than 40% of all patients met the composite endpoint for pain and stool consistency, and this response continued for the remaining 12 weeks of treatment (Figure 4). During the 12-week period, 17% titrated up to a

**Table 4.** Alosetron Versus Traditional IBS-D Treatments: Healthcare Utilization\*

Resource Use	Alosetron Mean $\pm$ SE (range)	Traditional Therapy Mean $\pm$ SE (range)	P Value
All Physician Visits	3.8 $\pm$ 0.1 (0-43)	4.5 $\pm$ 0.3 (0-61)	.032
IBS-Related Visits	0.7 $\pm$ 0.0	1.1 $\pm$ 0.1 (0-27)	.0006
All Medications	9.2 $\pm$ 0.2 (0-68)	9.5 $\pm$ 0.6 (0-60)	0.638
IBS Prescriptions per Week	1.0 $\pm$ 0.1 (0-14)	0.9 $\pm$ 0.1 (0-8)	.644
IBS Over-the-Counter Agents per Week	0.3 $\pm$ 0.0 (0-4)	0.7 $\pm$ 0.1 (0-21)	<.001

\*Results were similar for patients with restriction of daily activities, who used slightly more resources overall.

IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome-diarrhea; SE, standard error.

Adapted from Chey WD et al. DDW abstract Tu1386. *Gastroenterology*. 2013;76(6).<sup>2</sup>

dosage of 1 mg twice daily based on their response to the lower doses, and 22% titrated down to a dosage of 0.5 mg once a day. These dosage changes highlight the fact that a significant subset of patients with IBS-D can benefit from very low dosing with alosetron. Patients in the alosetron arm achieved significant and clinically meaningful improvements in both abdominal pain and stool consistency. Over 45% of patients met the FDA recommended composite endpoint of demonstrating efficacy on more than 50% of weeks throughout the study.<sup>9</sup> Additionally, significant improvements were observed compared with baseline for a variety of IBS-related complaints, including abdominal pain, stool consistency, stool frequency, and urgency. Pain relief of at least 30% was reported by 46% of patients at Week 4 and by 63% of patients at Week 12. There was improvement in stool consistency by at least 1 point in 59% of patients at Week 4 and 71% at Week 12. The number of stools per day was significantly reduced from 3.7 per day at baseline to 2.9 per day at Week 4 and 2.8 per day at Week 12. Importantly, this study found significant improvements in the percentage of days in which patients experienced fecal incontinence. Gastroenterologists are well aware that fecal incontinence is one of the major determinants of poor quality of life in patients with IBS-D. Therefore, the finding that alosetron reduced fecal incontinence shows an important advantage for this drug.

This trial also reported improvements in quality of life in all domains of the IBS-QOL instrument and on work productivity, confirming results from other studies.<sup>10</sup> Treatment satisfaction increased by approximately 2.5 points on a 7-point scale as assessed by both patients and physicians. In clinical practice, patients receiving alosetron were also less likely to use other healthcare resources (Table 4).

In conclusion, the totality of data from randomized controlled trials of up to 1 year in duration, as well as comparative effectiveness trials, clearly demonstrate the benefits of alosetron for women with IBS-D who have not improved with standard therapies. Significant improvements with alosetron treatment have been observed for multiple IBS endpoints, including global IBS symptoms, fecal incontinence, quality of life, work productivity, and treatment satisfaction.

### Acknowledgment

*Dr Chey is a consultant for AstraZeneca, Asubio, Ferring, Forest Laboratories, Ironwood Pharmaceuticals, Perrigo, Prometheus, SK, Salix, Sucampo, and Takeda. He has received research grants from Ironwood and Prometheus.*

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# Reassessing Alosetron Risk-Benefit Based on the Latest Postmarketing Safety Data

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### Background

As previously discussed, alosetron has very good efficacy vs placebo,<sup>1-3</sup> but concerns have been raised regarding its safety profile. Alosetron was first approved by the FDA in 2000. After the introduction of alosetron, it

was associated with postmarketing reports of ischemic colitis and serious complications of constipation. These reports led to its voluntary withdrawal in November 2000. In 2002, alosetron was reintroduced under a risk management program, and it was restricted to women with severe IBS-D who had failed conventional therapy.

**Table 5.** Postmarketing Reports of Ischemic Colitis and Complications of Constipation Associated with Alosetron: Reported and Adjudicated Incidence Rates

	Before June 2002 (before reintroduction/prior to the risk management program)*	November 2002–December 2011 (reintroduction under the risk management program)
Number of Prescriptions	586,000	341,784
Patient-Years of Alosetron Exposure <sup>†</sup>	48,829	28,084
<b>Ischemic Colitis<sup>‡</sup></b>		
Reported Incidence Rate (pre-adjudication)	1.70	1.53
Adjudicated Incidence Rate (probable/possible)	0.96	1.03
<b>Complications of Constipation<sup>‡</sup></b>		
Reported Incidence Rate (pre-adjudication)	2.00	0.93
Adjudicated Incidence Rate	0.59	0.25

\*Safety database of adverse events reported as of February 18, 2002 reported by Chang L et al. *Am J Gastroenterol.* 2006;101(5):1069-1079.<sup>6</sup>

<sup>†</sup>Each prescription is considered to represent 30 days of alosetron use.

<sup>‡</sup>Per 1,000 patient-years exposure.

Adapted from Tong K et al. *Therap Adv Gastroenterol.* 2013;6(5):344-357.<sup>8</sup>

**Table 6.** Comparison of Characteristics for Confirmed Cases of Ischemic Colitis From Postmarketing Data Before Alosetron Withdrawal\* and After Reintroduction

	Before June 2002 (before reintroduction/prior to risk management program)	November 2002–December 2011 (reintroduction under the risk management program)
Prescribing time span	10 months	109 months
Sex	57 female/1 male	29 female
Median age, years (range)	55 (25–80)	55 (22–81)
≥65 years	23%	17%
Median time to onset, days (range)	14 (0.5–136)	114 (3–2920)
<b>Presentation</b>		
Abdominal pain	79%	90%
Hematochezia or bloody diarrhea with abdominal pain	67%	72%
Concurrent constipation	24%	21%
<b>Outcomes</b>		
Deaths	0%	0%
Intestinal surgery	5.2%	1.7%
Transfusion	1.7%	0%
Hospitalization	67%	48%
Resolved or improved	77.5%	100%
Unresolved	7%	0%
Unknown	15.5%	0%

\*Data for period before withdrawal reported by Chang L et al. *Am J Gastroenterol.* 2006;101(5):1069-1079<sup>6</sup> and Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Subcommittee Background Package. April 23, 2002. US Department of Health and Human Services, Food and Drug Administration.<sup>9</sup>

Adapted from Tong K et al. *Therap Adv Gastroenterol.* 2013;6(5):344-357.<sup>8</sup>

In 2010, the risk management plan was converted to a REMS program.

The most studied therapeutic dosage of alosetron is 1 mg twice daily, which was originally approved in 2000. Under the REMS, the recommended starting dosage of alosetron is 0.5 mg twice daily. After 1 month, the dosage can be increased to 1 mg twice daily depending on patient response.

## Epidemiology of Ischemic Colitis

Epidemiological studies have demonstrated an independent association between IBS and ischemic colitis. In 2011, Lewis examined published studies to identify the frequency and clinical characteristics of ischemic colitis associated with the use of alosetron and other serotonergic agents.<sup>4</sup> A review of IBS patients who were receiving alosetron or tegaserod showed that many who developed ischemic colitis had comorbid medical conditions or were taking additional medications that have been associated with ischemic colitis. Compared with healthy controls, the background risk of ischemic colitis in IBS patients was increased 3-fold to 4-fold.<sup>5</sup> Thus, IBS itself appears to be associated with a greater risk for ischemic colitis regardless of alosetron use.<sup>4</sup>

## Current Postmarketing Safety of Alosetron Over 9 Years

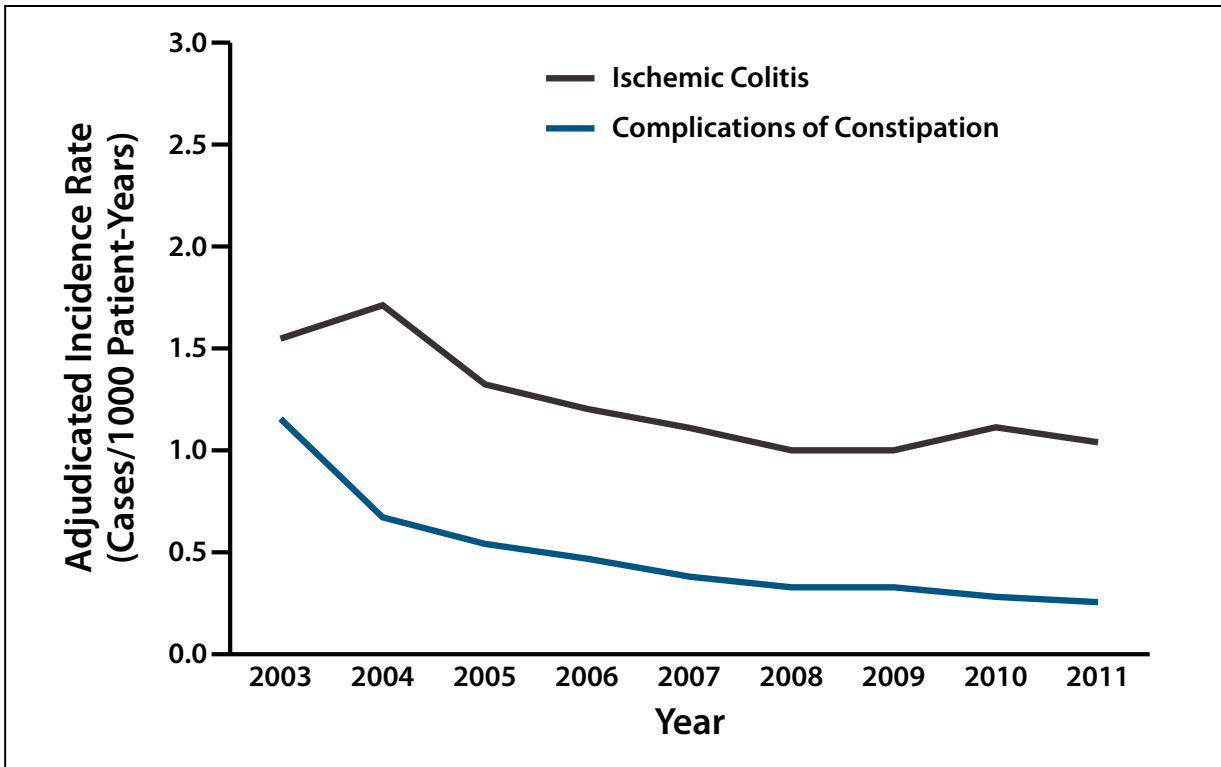
A study published in 2006 was the first to report on postmarketing cases of ischemic colitis and serious complications of constipation before and after the reintroduction of alosetron.<sup>6</sup> According to postmarketing surveillance data, the postadjudication rate of ischemic colitis was 1.1 per 1000 patient-years of alosetron use. The rate of serious complications of constipation in the postmarketing surveillance data was lower, at 0.66 per 1000 patient-years of alosetron use. Two follow-up studies also evaluated these associations.<sup>7,8</sup> The 2010 study by Chang and colleagues outlined the criteria used for medical evaluation and adjudication of cases of ischemic colitis and complications of constipation. Cases were assigned to 1 of 3 categories—insufficient evidence to support the diagnosis, possible ischemic colitis, or probable ischemic colitis—based on recommendations from the FDA.<sup>9</sup> Chang and colleagues reviewed data from 2002 to 2008, with the goal of adjudication of cases of ischemic colitis and serious complications of constipation since the risk management program was instituted.<sup>7</sup> The analysis showed that the absolute numbers of ischemic colitis and serious complications of constipation cases declined. However, the adjudicated incidence rates of ischemic colitis and serious complications of constipation remained similar. For ischemic coli-

tis, the incidence rate was 0.95 per 1000 patient-years, and it was 0.36 per 1000 patient-years for serious complications of constipation during the postmarketing period.

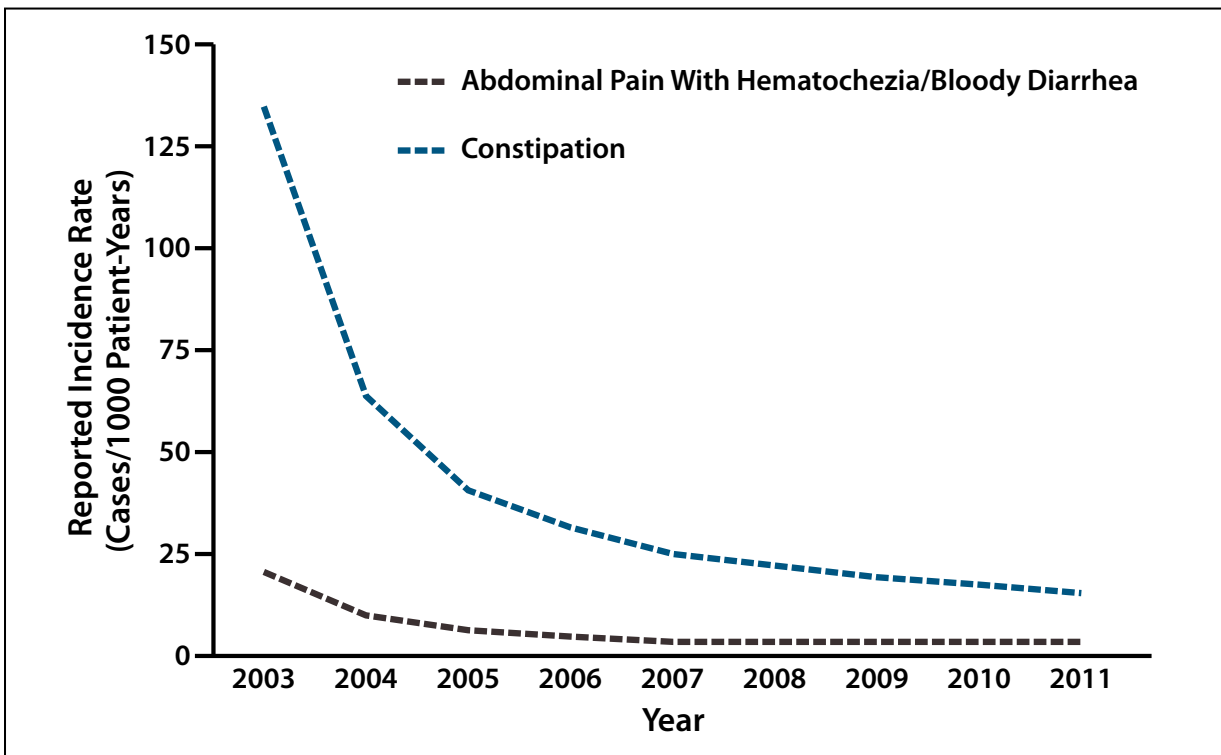
A more recent study by Tong and colleagues adjudicated postmarketing cases of ischemic colitis and complications of constipation, and evaluated temporal trends in alosetron postmarketing safety over 9 years under the risk management plan.<sup>8,10</sup> Table 5 shows the incidence rates of ischemic colitis and complications of constipation over 9 years, and Table 6 compares outcomes of patients with ischemic colitis before alosetron withdrawal vs after reintroduction. This study reviewed cases of ischemic colitis and serious complications of constipation under the RMP/REMS from 2002, when alosetron was reintroduced, to 2011. The cumulative adjudicated incidence rate of ischemic colitis was very similar to previous studies, at 1.03 cases per 1000 patient-years, suggesting that the incidence of ischemic colitis remained low and stable over time (Figure 5). The adjudicated incidence rate of serious complications of constipation was 0.25 cases per 1000 patient-years, which appears to have declined over time (Figure 5). Notably, reports of symptoms suggestive of ischemic colitis or complications of constipation (ie, abdominal pain accompanied by hematochezia/bloody diarrhea or constipation, respectively) also decreased during this time period (Figure 6).

More recently, while utilization and prescribing of alosetron have increased, the incidence rates of ischemic colitis and serious complications of constipation have remained low. The 9-year evaluation found that reports of symptoms of ischemic colitis, such as bloody stool and abdominal pain, have markedly declined from more than 20 cases per 1000 patient-years in 2003 to less than 10 cases per 1000 patient-years in 2008 through 2011.<sup>8</sup> According to postmarketing data, there were more reports of symptoms suggestive of ischemic colitis than of confirmed ischemic colitis (1.03 cases per 1000 patient-years). Over the 9-year period under the alosetron RMP/REMS, the incidence rates of confirmed cases of ischemic colitis and complications of constipation (Figure 5) have been much lower than incidence rates of symptoms suggestive of ischemic colitis (abdominal pain with hematochezia/bloody diarrhea) or complications of constipation (constipation) (Figure 6), implying that prescribers are effectively being educated on the signs and symptoms of ischemic colitis and complications of constipation and appropriate patient management.

In summary, recent postmarketing safety data demonstrate that the incidence rates of ischemic colitis and complications of constipation have remained rare and stable over time, and that serious outcomes have been mitigated over nearly a decade under the RMP/REMS



**Figure 5.** The cumulative adjudicated incidence rates of probable/possible ischemic colitis and complications of constipation in an analysis of temporal trends in alosetron postmarketing safety under the risk management program. Adapted from Tong K et al. *Therap Adv Gastroenterol.* 2013;6(5):344-357.<sup>8</sup>



**Figure 6.** Reports from the alosetron safety database of abdominal pain accompanied by hematochezia/bloody diarrhea, symptoms that may strongly indicate ischemic colitis or complications of constipation. Adapted from Tong K et al. *Therap Adv Gastroenterol.* 2013;6(5):344-357.<sup>8</sup>

program. Furthermore, the cases of ischemic colitis with alosetron have been reversible.<sup>8</sup> In addition, there have been no transfusions or deaths in adjudicated cases of ischemic colitis, and no deaths, surgeries, toxic megacolons, or intestinal perforations in adjudicated cases of complications of constipation. The 9-year safety analysis found that the incidence of serious complications of constipation appears to have decreased slightly compared to previous reports (0.25 vs 0.36 cases per 1000 patient-years).<sup>7</sup> Patients should be educated on and monitored for signs and symptoms of ischemic colitis and complications of constipation when treatment with alosetron is initiated.

### Managing Alosetron Use in Clinical Practice

Constipation can be minimized with a lower dose of alosetron. Patients are often instructed to stop alosetron therapy if they fail to have a bowel movement for 2 consecutive days. After they stop therapy, these patients typically experience diarrhea, at which point they can either restart alosetron at a lower dose or the same dose. This management approach has not been the subject of a clinical study, but it is based on data for cilansetron, another 5-HT<sub>3</sub> antagonist. Cilansetron was not approved by the FDA and was suspended from development. In studies of cilansetron, the incidence of ischemic colitis or serious complications of constipation increased in patients who had 2 consecutive days without a bowel movement.<sup>4</sup> In a review of probable/possible cases of ischemic colitis associated with alosetron, only a subgroup of patients (21%) had constipation at presentation.<sup>8</sup> These findings suggest that ischemic colitis does not necessarily occur in patients who are constipated.

### Acknowledgment

*Dr Chang has received consulting fees from Ferring, Forest Laboratories, Ironwood Pharmaceuticals, Takeda, Purdue Pharma, and Salix. She had performed contracted research for Ironwood Pharmaceuticals, Lexicon, and Tioga.*

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## Discussion

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**Brian E. Lacy, MD, PhD** As the previous discussions have shown, alosetron has much clinical trial data to support its use in women with severe symptoms of IBS-D who had an inadequate response to conventional IBS pharmacotherapy. Alosetron has been shown to improve fecal urgency, stool frequency, and stool consistency.<sup>1,2</sup> It also improves global symptoms of IBS and provided adequate relief of associated pain and discomfort.<sup>3-5</sup> I last counted about 89 published studies, and Dr Chey mentioned that 8 large, randomized, double-blind, controlled clinical studies have involved nearly 5000 patients. Why is alosetron not used as much as it should be in some patients, despite the strength of evidence about its efficacy compared with other medications? Also, how can the data be leveraged to select appropriate candidates for alosetron?

**William D. Chey, MD** I think there are 3 major issues that drive prescribing behavior in general and which apply to alosetron. First, all of the therapies for IBS that have been found to be effective in randomized controlled trials offer marginal efficacy. As I discussed, a meta-analysis of alosetron found that it offers a therapeutic gain of 15% over placebo,<sup>6</sup> and that is currently the upper limit of what can be expected with IBS drugs. Randomized controlled trials with other IBS drugs have shown a lower therapeutic gain of between 7% and 15% over placebo, which is marginal efficacy. Often doctors will wonder if a drug that offers 7% to 15% therapeutic gain over placebo is truly effective. The marginal benefits of IBS drugs over placebo are related to the heterogeneity of the pathogenesis of IBS; it is not that the drugs do not work, it is that they work for certain subgroups of IBS patients. Another concern is safety, which Dr Chang will discuss. Clinicians are very concerned about safety issues. The third issue, which is perhaps the most important one from a purely pragmatic standpoint, is formulary availability and cost. These are the 3 big drivers that hold back the wider use of alosetron.

**Brian E. Lacy, MD, PhD** Is there a lack of education among healthcare providers about alosetron as an option for severe IBS-D?

**Lin Chang, MD** General practitioners are usually educated about therapeutic agents by physicians or lecturers who use them. Many healthcare providers are not used to incorporating alosetron therapy in their practices because they have not learned about it from other physicians. A healthcare provider may not choose to join the prescriber program for alosetron. It is important, however, that such healthcare providers recognize patients who would benefit from alosetron therapy, and then refer such patients to physicians who do prescribe it.

**William D. Chey, MD** The labeling for alosetron creates some confusion by stating that the agent is only for women with severe IBS-D who have failed traditional therapies.<sup>7</sup> The meaning of “traditional therapies” will vary significantly from physician to physician. Does it include antibiotics, probiotics, and diet, for which the data are accruing? If you believe that it does, then alosetron gets relegated to pretty far down the list of treatment options.

When alosetron was first approved by the FDA, it was the only drug for the treatment of IBS-D. The marketplace for IBS therapies has become more crowded, and includes a number of relatively safe options. For example, a fairly robust body of literature is evolving regarding the role of diet as a treatment for IBS. Many clinicians are using probiotics, even in the absence of high-quality evidence. The numerous treatment options and regulatory requirements for use have hampered the widespread adoption of alosetron, both in terms of physicians’ familiarity with the agent and their understanding of where it fits in the treatment algorithm.

**Brian E. Lacy, MD, PhD** What is your perspective about the risks of other IBS-D medications used in gastroenterology?

**Lin Chang, MD** For IBS treatments, these agents have a fair number of associated adverse events. These adverse events often dictate whether an agent is used and at what dosage. Antispasmodics are one of the most commonly used agents for IBS. They are associated with dry mouth, some sedation, and even constipation if taken regularly. These concerns might lead to lowering of the dose or to use on an as-needed basis. Because of adverse events, care is required in using some of these agents. For example, a physician might not use antispasmodics or tricyclic agents regularly because patients with IBS-C experience constipating adverse events. Because the constipation that occurs with tricyclic agents has clearly been shown to be associated with adverse events, the dose is lowered. Sometimes adverse events lead to discontinuation of the treatment. Although tricyclics are effective, their risks and benefits must be weighed.

Tegaserod, which was removed from the market in 2007, had been thought to have a fairly good safety profile until a pooled FDA analysis showed an 11-fold increase (vs placebo) in the risk of cardiovascular events.<sup>8</sup>

**Brian E. Lacy, MD, PhD** Let's talk about alosetron safety data. As I mentioned, studies have shown that patients with IBS are willing to tolerate risk of adverse events in exchange for symptom improvement.<sup>9</sup> That being said, do we have a somewhat skewed perspective of the safety of alosetron?

**Lin Chang, MD** When alosetron was first approved, almost 600,000 prescriptions were written for IBS. However, some of these prescriptions were not for the appropriate target population: female patients with IBS-D. Alosetron was prescribed for patients with various IBS subtypes, different ages, and different medical histories. Healthcare providers were then taken aback by the increased reports of adverse events of complications of constipation and ischemic colitis. Physicians are now hesitant to use any agent to treat IBS because this disease is considered "benign," even though we know that it is associated with a burden on daily activities and quality of life. Serious adverse events, particularly ischemic colitis, are considered more morbid than IBS. In addition, many physicians probably became concerned about any legal issues that might arise if a serious adverse event developed in a patient taking alosetron.

Because alosetron was withdrawn and reintroduced, many physicians, particularly younger ones, are not knowledgeable about the drug. When I give presentations, some physicians will say that they have not even heard of the drug. However, as a recent study has shown, prescriptions for alosetron are now increasing.<sup>10</sup> And, based on the most recent evidence on postmarketing safety of alosetron

over nearly a decade under a risk management program, incidence rates of ischemic colitis and complications of constipation are still rare and have remained rare over time. When alosetron is used in the right patients at the right dose, patients are educated about its use, and adverse events are well managed, patients do well on this drug.

**Brian E. Lacy, MD, PhD** What is the role of rifaximin?

**William D. Chey, MD** Rifaximin is a broad-spectrum, nonabsorbable antibiotic.<sup>11</sup> Several randomized controlled trials support the use of rifaximin as a treatment for IBS.<sup>11-13</sup> Short-term treatment with rifaximin appears to be safe and well tolerated. Although rifaximin clearly provides benefit to a subset of IBS sufferers and, as such, may have a place in the IBS treatment paradigm, it is important to recognize that the therapeutic gain over placebo is approximately 10%, so many patients will require other treatments. Also, as mentioned, rifaximin is still not FDA-approved for IBS. An additional re-treatment trial is under way, and I think it is fair to say that we are all eagerly awaiting results from this study.<sup>14</sup>

**Brian E. Lacy, MD, PhD** What are the adverse events associated with rifaximin?

**Lin Chang, MD** The FDA has expressed concerns about how the drug should be used in re-treating patients with recurrent symptoms. Studies are ongoing to assess the efficacy of re-treatment with rifaximin vs placebo. A post hoc pooled safety analysis of 1932 patients with nonconstipation IBS from 2 phase 3 and 1 phase 2B randomized, double-blind, placebo-controlled studies showed that safety and tolerability were similar with rifaximin and placebo.<sup>15</sup> The rate of any treatment-emergent adverse event was 53% for both rifaximin and placebo, and the rate of serious treatment-emergent adverse events was 2% for each group, as was the rate of discontinuation. The rates of GI-symptom adverse events were 18% with rifaximin vs 20% with placebo. Rates for nausea, abdominal pain, diarrhea, and vomiting were similar and low, ranging from 2% to 4% with rifaximin and 2% to 5% with placebo. This study collected and evaluated data on adverse events that occurred both during treatment and posttreatment. Non-GI adverse events were headache and upper respiratory infection. The rates of these adverse events were also similar between the rifaximin group and the placebo group, at approximately 5% or less. In contrast to results of short-term studies, results of long-term safety data for rifaximin in IBS patients have not been reported.

A main problem with rifaximin is the subsequent symptom relapse rate after it is stopped. Patients who

benefit from treatment with alosetron usually stay on the medication. It has sustained efficacy.

**Brian E. Lacy, MD, PhD** As we have discussed, there are several misconceptions regarding the efficacy and safety data of alosetron. What are some other common misconceptions about the management of IBS-D?

**William D. Chey, MD** A misconception among most physicians is that celiac disease is more common than microscopic colitis in patients with IBS-D. This belief is largely driven by the worldwide literature, which suggests that the prevalence of celiac disease amongst IBS patients is up to 5%. In the United States, however, this does not appear to be true. Our prospective endoscopic trial reported a prevalence rate of approximately 1.5% for microscopic colitis in a population of nonconstipated IBS patients.<sup>16</sup> By comparison, the prevalence of celiac disease was 0.4% in nonconstipated IBS patients and controls.<sup>17</sup> Remember that patients with microscopic colitis tend to be older than 40 years and female. In fact, in our study, women with IBS-D who were older than 40 years had a microscopic colitis prevalence of 2.5%. Therefore, random biopsies should be obtained in all IBS-D patients undergoing colonoscopy, particularly if they are female and older than 40 years.

**Lin Chang, MD** Another misconception is that alosetron-associated ischemic colitis is associated with a high incidence of deaths. The data show that this is not true. Ischemic colitis associated with alosetron has been shown to be reversible, and it is not the same as chronic mesenteric ischemia or acute mesenteric ischemia. It is, however, an adverse event of concern, and patients should be monitored for it. But the idea that adverse events that occur while on alosetron are fatal has not been supported by evidence-based studies. In reality, there have been no deaths resulting from confirmed ischemic colitis cases associated with alosetron.<sup>10</sup>

**William D. Chey, MD** In addition, it is sometimes thought that ischemic colitis is dose-dependent in patients receiving alosetron. Constipation is dose-dependent, but ischemic colitis is idiosyncratic.

**Brian E. Lacy, MD, PhD** Another misconception is that IBS-D occurs only in women. This is not true; men are affected as well. Finally, there is the misconception that once a person has IBS-D, it is going to progress to Crohn's disease, ulcerative colitis, or even cancer (Table 7).<sup>18</sup> There are no data to support this misconception, but it is prevalent and makes patients unnecessarily nervous and fearful.

**Table 7.** Patient Misconceptions About IBS

15% believe that IBS will turn into cancer
22% believe that IBS increases the risk of developing cancer of the colon or rectum
30% believe that IBS will turn into Crohn's disease

IBS, irritable bowel syndrome.

Data from Lacy BE et al. *Aliment Pharmacol Ther.* 2007;25(11):1329-1241.<sup>18</sup>

### Acknowledgments

*Dr Lacy is a co-investigator for the NIH Functional Dyspepsia Treatment Trial. In the last 2 years, he has served on the scientific advisory boards of Ironwood, Takeda, and Prometheus. Dr Chang has received consulting fees from Ferring, Forest Laboratories, Ironwood Pharmaceuticals, Takeda, Purdue Pharma, and Salix. She had performed contracted research for Ironwood Pharmaceuticals, Lexicon, and Tioga. Dr Chey is a consultant for AstraZeneca, Asubio, Ferring, Forest Laboratories, Ironwood Pharmaceuticals, Perrigo, Prometheus, SK, Salix, Sucampo, and Takeda. He has received research grants from Ironwood and Prometheus.*

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## Conclusion

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Healthcare providers of all specialties evaluate and treat patients with IBS. For many patients, unfortunately, IBS is a chronic disorder that requires long-term treatment. Therapeutic management decisions for patients with IBS-D should be based on individual symptoms of abdominal pain, diarrhea, urgency, and incontinence. An assessment of global symptoms should be performed, and the healthcare provider should evaluate both the severity of the patient's symptoms and their affect on his or her quality of life. Symptom severity can be assessed using a validated scale or measured using global symptom responses. Importantly, severe IBS-D is much more common than initially thought, and because severity affects treatment decisions, failure to adequately assess disease severity may lead to sub-optimal treatment choices and poorer patient outcomes. Finally, decisions on therapy should be evidence-based and not based on intuition or anecdotal experience.

To assist IBS patients in choosing an appropriate therapy, healthcare providers should always ask patients 3 key questions. One, what fears or concerns do you have about your condition? Two, what are your goals? Three, are you a risk-taker, and, if so, what type of risks are you willing to take with IBS-directed therapies? The first question is critical, as a number of misconceptions exist regarding the treatment and diagnosis of IBS, and these misconceptions need to be corrected. As mentioned above, 30% of IBS patients believe that IBS turns into Crohn's disease. The second question is important because treatment goals vary from patient to patient, and although 2 patients may have

virtually identical symptoms, their goals may be quite different. Finally, all therapies have some risk associated with them. It is important to understand the risk of the therapies recommended and to understand the willingness of your patient to take medication-associated risks.

Fortunately, a variety of treatment options exist for women with IBS-D. These options range from dietary interventions to over-the-counter remedies, to prescription medications, to alternative and complementary therapies. When discussing these treatment options with a patient, healthcare providers should rely upon published studies, meta-analyses, and guidelines to present the best evidence-based treatment approach. Healthcare providers should also understand the risks and benefits associated with individual treatment options. Fortunately, for women with persistent IBS-D symptoms, a large body of evidence supports the use of alosetron, the only FDA-approved medication for women with IBS-D who have failed other IBS therapy. Although some healthcare providers have misconceptions about the efficacy or safety of alosetron, multiple large randomized placebo-controlled trials, as well as a number of meta-analyses, have consistently shown that alosetron is safe and efficacious at improving the multiple symptoms of IBS-D in women.

### **Acknowledgment**

*Dr Lacy is a co-investigator for the NIH Functional Dyspepsia Treatment Trial. In the last 2 years, he has served on the scientific advisory boards of Ironwood, Takeda, and Prometheus.*



# Slide Library

## Irritable Bowel Syndrome (IBS)

- The most common functional GI disorder encountered by all healthcare providers
- Characterized by the presence of abdominal pain or discomfort that is temporarily relieved by defecation
- Can present with constipation (IBS-C), diarrhea (IBS-D), or mixed constipation and diarrhea (IBS-M)

14 gastroenterology

## Rome III Criteria for the Diagnosis of IBS

- The patient must have recurrent abdominal pain or discomfort for at least 3 days per month in the last 3 months with symptom onset at least 6 months before diagnosis and the presence of at least 2 of the following:
  - Symptoms improve with defecation
  - Onset is associated with change in stool frequency
  - Onset is associated with change in stool appearance

## Conventional Pharmacotherapy for IBS-D

- Over that past several decades, conventional pharmacotherapy for IBS-D has been largely focused on individual symptoms, rather than relief of global IBS symptoms
- Conventional agents include antidiarrheal agents, such as loperamide or diphenoxylate-atropine, and smooth muscle antispasmodics, such as hyoscyamine or dicyclanine
- No good data from well-designed randomized placebo-controlled trials demonstrate that these agents are effective for treating IBS-D symptoms
- The safety and tolerability of these agents in IBS-D have not been established in large, randomized, placebo-controlled trials

## Questions for Patients When Selecting Therapy for IBS

- What fears or concerns do you have about your condition?
- What are your goals?
- Are you a risk-taker, and, if so, what type of risks are you willing to take with IBS-directed therapies?

## Alosetron: Background in IBS-D

- First approved by the FDA for the treatment of IBS-D in women in February 2000
- Voluntarily withdrawn from the US market in November 2000 based on concerns regarding a possible association with serious complications of constipation and ischemic colitis
- Returned to the marketplace in 2002 because of pleas from IBS advocacy groups to make it available again for patients

\*FDA. L30. Final 04/22/04. Approval of IBS-C. <http://www.fda.gov/cder/rdmt/ibs040204.htm>

## Alosetron in IBS-D

- Addresses 2 broad categories of medical needs in patients with IBS-D:
  - Improves multiple individual symptoms, such as abdominal pain, stool frequency, stool consistency, urgency, and episodes of incontinence
  - Improves global IBS symptoms and health outcomes, such as quality of life, workplace productivity, and treatment satisfaction

### Alosetron: Data From an Observational Study

- Total enrolled 134 women with IBS-D, with 81% receiving alosetron 0.3 mg twice daily, 12% receiving 0.3 mg once daily, and the rest receiving some combination of 1-mg dosing. The patients received alosetron for 12 weeks.
- Significant improvements were observed compared with baseline for a variety of IBS-related complaints, including abdominal pain, stool consistency, stool frequency, and urgency. Importantly, this study found improvements in the percentage of days in which the patients reported fecal incontinence.
- Improvements in quality of life in all domains of the IBS-QOL instrument and on work productivity.

Laini KE et al. Real-world use of alosetron: results of a multi-center observational study. *GGN Abstracts* (2013). *Gastroenterology Abstracts*. 2013;124:1026.

Laini KE et al. Effects of bowel outcomes with alosetron in clinical practice: results from a multicenter observational study. *GGN Abstracts* (2013). *Gastroenterology Abstracts*. 2013;124:1026.

### Alosetron Vs Traditional IBS Therapy

- The patients who were treated with alosetron reported significantly fewer office and clinic visits for any health problems, as well as for IBS.
- Alosetron-treated patients used significantly fewer over-the-counter medications for IBS, had fewer days of lost work productivity, and reported less restriction of outdoor activities compared with patients who received traditional therapy.
- Consistent with previous results, alosetron improved quality of life scores for all 9 domains of the IBS-QOL.
- Global IBS symptoms improved in a significantly greater proportion of patients treated with alosetron than in those on conventional therapies.

IBS-QOL: Irritable Bowel Syndrome Quality of Life Questionnaire. *Abb from Chee RZ et al. IBS-QOL Abstract* (2008). *Gastroenterology Abstracts*. 2013;124:1026.

### Alosetron: Safety Profile After Reintroduction

- The cumulative adjudicated incidence of ischemic colitis was very similar to previous studies, at 1.03 cases per 1000 patient-years, suggesting that the incidence of ischemic colitis remained low and stable over time.
- The adjudicated incidence rate of serious complications of constipation was 0.25 cases per 1000 patient-years, which appears to have declined over time.
- Symptoms of ischemic colitis, such as bloody stool and abdominal pain, have markedly declined to less than 10 cases per 1000 patient-years.

Yang H et al. *Ther Adv Gastroenterol*. 2012;6(3):144-167.

### Managing Alosetron Use in Clinical Practice

- Constipation can be minimized with a lower dose of alosetron.
- Patients are often instructed to interrupt alosetron therapy if they fail to have a bowel movement for 2 consecutive days.
- After they stop therapy, these patients typically experience diarrhea, at which point they can either restart alosetron at a lower dose or the same dose.

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