Published in final edited form as:

Am J Gastroenterol. 2012 November ; 107(11): 1726–1729. doi:10.1038/ajg.2012.325.

Linacotide: Promising IBS-C Efficacy in an Era of Provisional Study Endpoints

Gregory S. Sayuk, MD, MPH^{1,2,3}

¹Division of Gastroenterology, Washington University School of Medicine, St Louis, Missouri, USA

²Department of Psychiatry, Washington University School of Medicine, St Louis, Missouri, USA

³Saint Louis Veterans Affairs Medical Center-John Cochran Division, Saint Louis, Missouri, USA

Abstract

Recent disappointing developments in the pharmacotherapy of irritable bowel syndrome (IBS) have not dampened the enthusiasm surrounding linacotide, a novel guanylate cyclase-C agonist for the management of constipation-predominant IBS (IBS-C). Two recent phase 3 studies reporting on a single, daily dose of linacotide are presented in this issue of the *American Journal of Gastroenterology*. Importantly, these studies are the first to examine a provisional Food and Drug Administration (FDA) combined response endpoint for IBS-C, which mandates improvements of both abdominal pain and defecatory symptoms. Potential limitations of this FDA endpoint relate to a lack of inclusion of other potentially important IBS symptoms and an inability to directly compare findings with other recent IBS-C trials. Both studies successfully reached this endpoint in approximately one-third of study subjects, resulting in numbers needed to treat (NNT) of five to eight, to achieve an FDA responder. Individual symptom responses to linacotide were seen in nearly 50% of participants, and potential explanations for these discrepancies when compared with the FDA endpoint are offered. Adequate relief measures also were assessed and, with NNTs of 3.4–6.8, compared favorably with other contemporary IBS-C studies. Overall, both linacotide trials found the medication to be safe in terms of serious adverse events, though the secretagogue mechanism of action led to diarrhea in approximately one in five subjects. Together, these studies inspire several other important questions regarding linacotide, including its role in the management of IBS-C relative to existing treatment options, such as lubiprostone. Greater clinical use of linacotide will reveal whether the observed responses measured with the FDA provisional endpoint will translate into real-world experiences of improvement in IBS patients.

“In seeking absolute truth we aim at the unattainable and must be content with broken portions.”—Sir William Osler

The last decade has been a proverbial roller-coaster ride for irritable bowel syndrome (IBS) patients and the providers who care for them. We have experienced the exhilarating highs of exciting, new IBS treatment developments, all too often followed by the free fall of promising medications failing to attain the Food and Drug Administration (FDA) approval (1,2), being withdrawn from the US market over adverse-effect concerns (3,4) or

© 2012 by the American College of Gastroenterology

Correspondence: Gregory S. Sayuk, MD, MPH, Division of Gastroenterology, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8124, St Louis, Missouri 63110, USA. gsayuk@im.wustl.edu.

CONFLICT OF INTEREST

Gregory Sayuk wrote the initial draft, performed the data interpretation, and is responsible for the content of this manuscript. Gregory Sayuk is on the Takeda speaker bureau, and receives research funding from the US National Institutes of Health (NIH)-K23 DK084113.

complicated by stipulations of the Prescriber Program enrollment for use (5,6). Re-equilibrating from this dizzying trip, we now find that, presently, lubiprostone stands alone as the only remaining FDA-approved medication for use in constipation-predominant IBS (IBS-C) patients (7).

With this series of enthralling climbs and rapid descents of IBS therapeutic options etched indelibly in the minds of the IBS community, it is with cautious enthusiasm that we look forward to the potential FDA approval of a novel guanylate cyclase-C agonist, linaclotide, for the management of IBS-C symptoms (8). In this issue of the *American Journal of Gastroenterology*, two complementary papers provide important phase 3 randomized, controlled data on linaclotide in treatment of IBS-C. By design, these studies share several similarities; each reports on the once-daily 290- μ g oral linaclotide or placebo in large samples of approximately 800 IBS-C patients, and both apply a new, provisional FDA co-primary endpoint for IBS-C requiring improvements in abdominal pain intensity and complete spontaneous bowel movements, or CSBMs (9). The main design differences in these two trials relate to study duration, with Chey *et al.* reporting on a 26-week total treatment period, whereas Rao *et al.* treated IBS-C patients with linaclotide or placebo for 12 weeks, followed by a 4-week randomized withdrawal period. Through the data collected in these two clinical trials, the gastroenterology community now seeks to answer several critical questions regarding linaclotide as a potential new treatment option in IBS-C.

Given the recent troubling experiences with adverse events relating to IBS pharmacotherapies, the foremost amongst the priorities must be an effort to convincingly address any concerns about the safety of linaclotide. From a pharmacokinetic perspective, the initial reassurances regarding linaclotide's safety emerged from animal model studies, suggesting a very low oral bioavailability of linaclotide and its active metabolites (0.1%) (10). These data seemingly would make the systemic toxicity that has plagued some of linaclotide's predecessors less likely. The clinical trial data presented in this issue of *American Journal of Gastroenterology*, along with phase 2b and phase 3 data on linaclotide in chronic constipation patients, now represent a collective experience of over 500 patient-years of linaclotide therapy (11–13). Across these studies, serious adverse events were few (< 1.0% of subjects), were not significantly greater than rates seen with placebo, and were in no case conspicuously linked to linaclotide. However, in the current trials, treatment-emergent adverse events (TEAEs) were reported by over one-half of those receiving linaclotide, the most noteworthy being a statistically significant greater incidence of diarrhea in one of five subjects. These observations relate to the secretagogue mechanism of the drug (14), and reflect the relatively narrow therapeutic window common to such agents, including the chloride-channel agonist, lubiprostone (15). Although minor TEAEs led to medication discontinuation in only a small percentage of those treated with linaclotide, more widespread clinical experience will further clarify to what extent these minor adverse effects may limit patient acceptance of this medication.

Safety concerns addressed, we can now consider the more interesting questions relating to linaclotide efficacy in IBS-C. Here, all eyes initially should focus on the combined FDA "response" endpoint. After all, the FDA approval of linaclotide for use in IBS-C (currently under FDA review) will hinge largely on this key endpoint, mandating improvements in both abdominal pain intensity ($\geq$ 30% from average daily worst pain score) and complete spontaneous bowel movements ($\geq$ 1 CSBM from baseline) for at least one-half of the total study weeks (9). In short, both studies successfully demonstrated nearly identical FDA response rates of just over one-third of IBS-C subjects receiving linaclotide. Accounting for placebo responses, these data suggest that around five to eight IBS-C subjects would need to be treated with linaclotide to achieve a single FDA-defined responder. Placing this FDA response data on linaclotide in the context of other contemporary IBS clinical trials is

challenging, as this provisional FDA endpoint represents a departure from previous IBS studies conducted over the past decade. Earlier IBS clinical trials predominantly utilized either a binary (yes/no) endpoint of “adequate relief” or “satisfactory relief” with therapy (16–18), or a Likert-based “subject global assessment of relief” (19). Such global assessment items, although reproducible and responsive to changes in clinical status, have been criticized for a lack of detailed assessment of individual IBS symptoms (20 – 24). In 2010, the FDA endorsed a co-primary IBS response endpoint that comprised both abdominal pain intensity and defecation measures (9). This new endpoint was justified on the grounds that IBS is a symptom-based diagnosis, which, by definition, involves abdominal pain/discomfort in association with defecatory issues (25); thus, it was decided that primary outcome measures should systematically assess each of these core symptoms individually. One distinct disadvantage to this combined FDA endpoint is the presumption that abdominal pain intensity and bowel frequency are the symptoms uniformly held by all IBS patients as the principal targets of any therapeutic intervention. However, clinical intuition suggests, and indeed objective studies confirm, that IBS patients experience difficulties with a variety of symptoms, including bloating, straining, flatulence, and altered stool consistency, to name a few (26–28). Some IBS patients do not identify with the experience of pain at all, rather relating symptoms of “discomfort” or “cramping”. When pain is endorsed, it is often a multidimensional experience, not limited to a spectrum of intensity alone, but also qualified by other key descriptors, such as bothersomeness, predictability, frequency, and impact on function (26). Considering the complexity and diversity of the IBS symptom experience, a contrarian view might hold that although admittedly less specific, the global IBS measures supplanted by the FDA co-primary endpoint are actually superior at capturing holistically the IBS symptom experience.

In this climate of shifting endpoints, how should the clinician then interpret these data on the efficacy of linaclotide relative to our IBS-C patients? Some additional insights may be gained by first examining the data regarding individual IBS symptoms. The data on linaclotide’s impact on bowel frequency are reasonably straightforward; the studies by Rao *et al.* (29) and Chey *et al.* (30) find that the previously observed benefit of linaclotide in chronic constipation extends to IBS-C populations (11). Both IBS-C trials observed a mean increase of over 2 CSBMs a week with linaclotide, an impressive gain from a baseline mean of only 0.2 CSBMs per week at study onset. Applying the FDA definition of “improvement” in bowel frequency as an increase ≥ 1 CSBM per week from baseline in at least 6 of the first 12 of the study weeks (9), both studies achieved this endpoint in just less than one-half of linaclotide recipients. Very respectable numbers needed to treat (NNT) result, and suggest that four to five patients would need to be treated with linaclotide to achieve one FDA-defined improvement in bowel frequency. The Chey *et al.* study also suggests that this bowel frequency response to linaclotide is durable, with nearly 90 % of the overall constipation benefit seen in the first 12 weeks still persisting at week 26.

In terms of pain response, both phase 3 trials demonstrated that significantly greater numbers of IBS-C patients reported decreases in maximal pain intensity (FDA defined as a $\geq 30\%$ improvement in abdominal pain intensity from baseline in 6 of 12 study weeks), with linaclotide compared with placebo. Chey *et al.* and Rao *et al.* consistently found that around 50 % IBS-C subjects treated with linaclotide reached this FDA pain-improvement endpoint. Recalling that 50 % of linaclotide recipients similarly reached the bowel frequency endpoint, one might initially conclude that the observed improvement in abdominal pain with linaclotide is simply a downstream effect of gains in intestinal transit and bowel frequency. However, this notion is dispelled by re-examining this data in the context of the combined FDA endpoint, where it was found that improvements in both abdominal pain and bowel frequency were reached only in one out of three patients receiving linaclotide. These discrepancies between the FDA-combined endpoint and individual symptom response rates

suggest that a number of linaclotide patients (around 16% overall, or one in three pain responders) will experience improvements in abdominal pain intensity without improvement in bowel frequency (Figure 1). These data allow for several interpretations. First, these findings could be viewed as providing indirect evidence in support of animal studies, suggesting a second benefit of linaclotide in the extracellular inhibition of pain fiber activity (31). On the other hand, some patients (14.5% of linaclotide recipients) seem to experience only laxative effects, without enjoying the benefit of a meaningful pain response. Drawing a firm conclusion from these data is even more of a challenge when considering the phase 3 data on linaclotide in chronic constipation. Lembo and colleagues (11) found that almost one-third of chronic constipation patients treated with linaclotide reported a decrease in abdominal discomfort, this in a condition not typically associated with visceral hypersensitivity (11,25). These observations highlight the need for additional research to better understand the pharmacology and mechanisms of action of linaclotide. Still, some of the uncertainty inherent in these observations will likely remain, in part relating to the challenge of optimally defining (and measuring) the core IBS symptoms of pain and abnormal defecation.

Finally, although assessments of additional IBS symptoms have been relegated to a status of lesser import as secondary endpoints, both phase 3 linaclotide studies nevertheless did examine several accessory IBS-C symptoms worth mentioning. In both reports, nearly 50% of IBS-C subjects endorsed significant decreases in abdominal discomfort, bloating, cramping, and fullness for at least one-half of the study weeks. Statistical improvements over placebo in straining, stool consistency, and constipation severity scores also were observed. Though these symptoms are important to the irritable bowel patient, measures of these symptoms remain unproven as independent variables in IBS-C clinical trials. As such, we continue to rely on validated global measures as proxy assessments of these accessory symptoms, in combination with core pain and defecatory symptoms. Each of the current protocols did collect global response data via an “adequate relief” question, and again found that approximately one-half of linaclotide patients reported adequate relief of symptoms in at least 6 weeks of the initial 12 study weeks. Accounting for placebo responders, NNTs of 3.4 – 6.8 to achieve adequate relief were calculated in the two studies. Adequate relief remains the best measure to allow for the comparison of these phase 3 results with linaclotide with the other recent studies of IBS-C, all of which employed global assessments of relief. With NNT from recent IBS clinical trials as a precedent (e.g., lubiprostone, NNT 12.8; tegaserod, NNT 7.9) the linaclotide data presented in these two studies should be compelling when reviewed by regulatory agencies (16,18,19,32).

Looking toward the future of linaclotide in the treatment of IBS-C, several important knowledge gaps remain. First, we need to more clearly establish the role of linaclotide in the context of the other IBS-C treatments, including lubiprostone. It will be important to learn whether linaclotide is superior to lubiprostone and, moreover, whether patients unresponsive to one of these agents will potentially benefit from switching to the other secretagogue. And, as linaclotide appears to confer a benefit to only a portion of IBS-C patients, gastroenterologists will need to establish a more precise understanding of who exactly the “linaclotide responders” are, not only in terms of bowel pattern and IBS symptom severity, but also relevant physiologic and non-gastrointestinal clinical factors, such as psychiatric comorbidity. Given the heterogeneity of symptom experiences among IBS patients, the ideal primary endpoint to study novel IBS treatments will likely never be fully unattainable. However, efforts of the Patient Reported Outcome Consortium are underway as a part of a joint public – private venture, in an attempt to bring greater clarity into IBS patient symptom experiences, and hopefully to improve future approaches to the assessment of IBS symptoms in the context of clinical trials (33). In the interim, real-world experiences will soon clarify for the gastroenterology community whether the objective improvement in portions of the

IBS-C symptom experience, as detected using the provisional FDA endpoint, will translate clinically into linaclotide's emergence as a new therapeutic agent promising "true improvements" in those living with IBS.

Acknowledgments

C. Prakash Gyawali, MD, MRCP and David Alpers, MD provided critical review of this manuscript.

References

1. Pimentel M, Lembo A, Chey WD, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med*. 2011; 364:22–32. [PubMed: 21208106]
2. Cremonini F, Lembo A. Rifaximin for the treatment of irritable bowel syndrome. *Expert Opin Pharmacother*. 2012; 13:433–40. [PubMed: 22251066]
3. Brinker AD, Mackey AC, Prizont R. Tegaserod and ischemic colitis. *N Engl J Med*. 2004; 351:1361–4. discussion 1361–4. [PubMed: 15385670]
4. Heading R, Bardhan K, Hollerbach S, et al. Systematic review: the safety and tolerability of pharmacological agents for treatment of irritable bowel syndrome--a European perspective. *Aliment Pharmacol Ther*. 2006; 24:207–36. [PubMed: 16842449]
5. Lewis JH. The risk of ischaemic colitis in irritable bowel syndrome patients treated with serotonergic therapies. *Drug Saf*. 2011; 34:545–65. [PubMed: 21663331]
6. US Food and Drug Administration (FDA). Lotronex (Alosetron Hydrochloride) Information. (cited 1 August 2012); available from: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm110450.htm>
7. US Food and Drug Administration (FDA). Amitiza (lubiprostone) Capsules. (cited 1 August 2012); available from: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116889.htm>
8. Roque MV, Camilleri M. Linaclotide, a synthetic guanylate cyclase C agonist, for the treatment of functional gastrointestinal disorders associated with constipation. *Expert Rev Gastroenterol Hepatol*. 2011; 5:301–10. [PubMed: 21651347]
9. US Department of Health and Human Services, US Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Guidance for Industry: Irritable Bowel Syndrome - Clinical Evaluation of Drugs for Treatment. May. 2012 (cited 1 August 2012); available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM205269.pdf>
10. Busby RW, Bryant AP, Bartolini WP, et al. Linaclotide, through activation of guanylate cyclase C, acts locally in the gastrointestinal tract to elicit enhanced intestinal secretion and transit. *Eur J Pharmacol*. 2010; 649:328–35. [PubMed: 20863829]
11. Lembo AJ, Schneier HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. *N Engl J Med*. 2011; 365:527–36. [PubMed: 21830967]
12. Johnston JM, Kurtz CB, Macdougall JE, et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. *Gastroenterology*. 2010; 139:1877–86. e2. [PubMed: 20801122]
13. Lembo AJ, Kurtz CB, Macdougall JE, et al. Efficacy of linaclotide for patients with chronic constipation. *Gastroenterology*. 2010; 138:886–95. e1. [PubMed: 20045700]
14. Bryant AP, Busby RW, Bartolini WP, et al. Linaclotide is a potent and selective guanylate cyclase C agonist that elicits pharmacological effects locally in the gastrointestinal tract. *Life Sci*. 2010; 86:760–5. [PubMed: 20307554]
15. Camilleri M, Bharucha AE, Ueno R, et al. Effect of a selective chloride channel activator, lubiprostone, on gastrointestinal transit, gastric sensory, and motor functions in healthy volunteers. *Am J Physiol Gastrointest Liver Physiol*. 2006; 290:G942–7. [PubMed: 16603730]
16. Camilleri M, Chey WY, Mayer EA, et al. A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome. *Arch Int Med*. 2001; 161:1733–40. [PubMed: 11485506]

17. Camilleri M, Mayer EA, Drossman DA, et al. Improvement in pain and bowel function in female irritable bowel patients with alosetron, a 5-HT₃ receptor antagonist. *Aliment Pharmacol Ther.* 1999; 13:1149–59. [PubMed: 10468696]
18. 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; 355:1035–40. [PubMed: 10744088]
19. Drossman DA, Chey WD, Johanson JF, et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome--results of two randomized, placebo-controlled studies. *Aliment Pharmacol Ther.* 2009; 29:329–41. [PubMed: 19006537]
20. Whitehead WE, Palsson OS, Levy RL, et al. Reports of “satisfactory relief” by IBS patients receiving usual medical care are confounded by baseline symptom severity and do not accurately reflect symptom improvement. *Am J Gastroenterol.* 2006; 101:1057–65. [PubMed: 16573774]
21. Schoenfeld P, Talley NJ. Measuring successful treatment of irritable bowel syndrome: is “satisfactory relief” enough? *Am J Gastroenterol.* 2006; 101:1066–8. [PubMed: 16696786]
22. Spiegel B, Camilleri M, Bolus R, et al. Psychometric evaluation of patient-reported outcomes in irritable bowel syndrome randomized controlled trials: a Rome Foundation report. *Gastroenterology.* 2009; 137:1944–53. e1–3. [PubMed: 19706292]
23. Mangel AW, Hahn BA, Heath AT, et al. Adequate relief as an endpoint in clinical trials in irritable bowel syndrome. *J Int Med Res.* 1998; 26:76–81. [PubMed: 9602985]
24. Mangel AW, Fehnel SE. End points in irritable bowel syndrome. *Expert Rev Gastroenterol Hepatol.* 2011; 5:293–5. [PubMed: 21651345]
25. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology.* 2006; 130:1480–91. [PubMed: 16678561]
26. Spiegel BM, Bolus R, Agarwal N, et al. Measuring symptoms in the irritable bowel syndrome: development of a framework for clinical trials. *Aliment Pharmacol Ther.* 2010; 32:1275–91. [PubMed: 20955447]
27. Spiegel BM, Bolus R, Harris LA, et al. Characterizing abdominal pain in IBS: guidance for study inclusion criteria, outcome measurement and clinical practice. *Aliment Pharmacol Ther.* 2010; 32:1192–202. [PubMed: 20807217]
28. Lackner J, Jaccard J, Baum C, et al. Patient-reported outcomes for irritable bowel syndrome are associated with patients’ severity ratings of gastrointestinal symptoms and psychological factors. *Clin Gastroenterol Hepatol.* 2011; 9:957–64. e1. [PubMed: 21699821]
29. Rao S, Lembo AJ, Shiff SJ, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. *Am J Gastroenterol.* 2012; 107:1714–24. (this issue). [PubMed: 22986440]
30. Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol.* 2012; 107:1702–12. (this issue). [PubMed: 22986437]
31. Castro J, Martin C, Hughes P, et al. A novel role of cyclic GMP in colonic sensory neurotransmission in healthy and TNBS-treated mice. *Gastroenterology.* 2011; 140:s538.
32. Tack J, Muller-Lissner S, Bytzer P, et al. A randomised controlled trial assessing the efficacy and safety of repeated tegaserod therapy in women with irritable bowel syndrome with constipation. *Gut.* 2005; 54:1707–13. [PubMed: 16020489]
33. US Food and Drug Administration (FDA). Critical Path Initiative. (cited 1 August 2012); available from: <http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm>

Figure 1.

The Food and Drug Administration (FDA) endpoints for abdominal pain intensity, bowel frequency, and the combined provisional FDA endpoint. The data illustrated reflect the combined 12-week phase 3 experience with linaclotide in irritable bowel syndrome (IBS)-C from Chey et al. and Rao et al. Although approximately one out of two patients treated with linaclotide achieved an improvement pain response *or* bowel frequency, only one out of three achieved the combined FDA response endpoint of *both* improved abdominal pain *and* bowel frequency. Smaller subsets (~15% subjects) experienced improvement in pain or bowel frequency.