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Oregon Health Authority

New Drug Evaluation: Linaclotide

Month/Year of Review: November, 2012
End date of literature search: November, 2012
Generic Name: Linaclotide
Drug Class: Prosecretory Gastrointestinal Agent
Brand Name (Manufacturer): Linzess® (Forest Laboratories, Inc.; Ironwood Pharmaceuticals, Inc.)

FDA Approved Indication: Treatment of irritable bowel syndrome with constipation (IBS-C) and for the treatment of chronic idiopathic constipation (CIC).[1]

Research Questions:
- Is linaclotide more effective than lubiprostone, laxatives, or other non-pharmacological agents for the reduction of constipation symptoms in IBS-C and CIC?
- Is linaclotide better tolerated than lubiprostone, the only other agent that is FDA approved for both non-emergency IBS-C and CIC?
- Are there specific populations for which linaclotide is better tolerated or more effective?

Conclusions:
- There is a moderate level of evidence that linaclotide reduces symptoms of constipation and pain associated with CIC and IBS-C. There is insufficient evidence to determine whether linaclotide improves clinical outcomes associated with health related quality of life.
- There are no comparative analyses published to date to determine if linaclotide is more effective or better tolerated than lubiprostone for CIC and IBS-C.
- It is unknown at this time whether linaclotide has the potential to cause the development of anti-linaclotide antibodies and cross-reaction with endogenous peptides.
- There is insufficient evidence to make conclusions of any improved efficacy or safety of linaclotide in specific subpopulations.

Recommendations:
- IBS and constipation are below the Oregon Health Plan line on the prioritized list. Include prior authorization to cover for only OHP covered diagnoses.

Background:
Irritable bowel syndrome (IBS) is a gastrointestinal disorder characterized by abdominal pain and discomfort that is accompanied by altered bowel habits.[2] The condition is the most frequently diagnosed GI disorder with a prevalence of 10-15% of the population in North America.[3] Up to 50% of all visits to the

gastroenterologist are for IBS, with female populations predominating at a ratio of 2:1 compared to males. While younger patients and women are more likely to be diagnosed with IBS, the disorder affects both sexes and all age groups. Patients may describe a constellation of symptoms ranging from cramping pain, diarrhea, alternating diarrhea and constipation, and periods of normal bowel habits interspersed with either constipation or diarrhea. Blood in the stool, nocturnal diarrhea, greasy stools or large volume diarrhea are not associated with IBS and indicate further investigation is warranted to isolate an organic cause.[2,3]

Irritable bowel syndrome with constipation is a subset of IBS that affects approximately one third of all IBS patients.[4] Symptoms that accompany IBS-C include abdominal bloating, hard stools, straining, and a sensation of incomplete evacuation.[2,4] Historical agents for the treatment of IBS-C included Tegaserod, a 5-HT4 partial agonist that was removed from the market in 2007 following increased cardiovascular events related to the medication; it is now only available as a prokinetic agent on an emergency IND basis. The only other approved agent in the U.S. for the treatment of IBS-C is lubiprostone, an E1 prostaglandin analogue chloride channel activator that increases chloride transport, intestinal fluid secretion and intestinal motility.[4] However, lubiprostone is only approved for adult, female patients with IBS-C. The most common side effect from lubiprostone is nausea, with an overall dose-related incidence ranging from 7 to 29%.[5] Lubiprostone is also approved for the treatment of chronic idiopathic constipation (CIC), a condition that is separate from IBS-C.

The symptoms of chronic idiopathic constipation are similar to IBS-C, i.e. bloating, straining during defecation, hard stools, abdominal discomfort, and a sense of incomplete evacuation.[2,6,7] Chronic idiopathic constipation is more prevalent in females, older individuals, and individuals of lower economic status or lower educational level.[7,8] The estimated prevalence of the disorder ranges from 4-20%, based on cross-sectional surveys of U.S. and European populations.[8] CIC by definition has no known cause, and is not associated with neurologic or metabolic disorders, lesions of the GI tract, or disorders such as diabetes or anorexia nervosa.

Constipation is the hallmark symptom that is shared between IBS-C and CIC. Insight into the placement of pharmacological therapy into the treatment algorithm for constipation may be gleaned from prucalopride guidance provided by NICE.[9] Although prucalopride is not available in the U.S., the guidance suggests a stepwise approach to the treatment of constipation before pharmacologic therapy is considered. First line options for treating constipation should focus on lifestyle and dietary modifications; short courses of laxatives may be administered if dietary and lifestyle modifications fail. A 2005 systematic review supports the use of specific laxatives in a stepwise fashion after first line options, citing adequate hydration, increased fiber intake, and nonstrenuous exercise as initial recommendations for treating constipation.[10] Reviewers analyzed data from randomized trials comparing non-pharmacological agents to placebo. The authors concluded that good evidence existed to support additional therapy with polyethylene glycol for the treatment of chronic constipation (Grade A). Moderate evidence supported the use of psyllium and lactulose (Grade B). There was insufficient evidence to support the use of bisacodyl, senna, milk of magnesia, or stool softeners for chronic constipation.

Patients who do not respond to lifestyle modifications or non-pharmacological treatment of IBS-C and CIC may wish to augment therapy with pharmacological options. Linaclotide is a new medication that will become available in the 4th quarter of 2012 as an additional treatment option for both IBS-C and CIC.[1] The agent is a synthetic, 14-amino acid peptide that is structurally related to endogenous guanylin peptides. The drug binds to and activates the guanylate cyclase C receptor on the luminal surface of intestinal epithelium. Once bound, activation of the receptor causes an increase in both intracellular and extracellular cGMP levels. Within intestinal epithelial cells, increases in cGMP initiate a signal-transduction cascade that activates the cystic fibrosis transmembrane conductance regulator. Ultimately, this causes secretion of chloride and bicarbonate into the intestinal lumen, leading to increased luminal fluid secretion and accelerated intestinal transit. FDA approved dosing includes linaclotide 290 mcg for irritable bowel syndrome with constipation, while the 145 mcg dose is indicated for

chronic idiopathic constipation.[1] Approved doses have been modified to reflect potencies determined through analytical analysis during product development and differ slightly from the doses reported in phase II trials.[12]

Clinical Efficacy:

A total of 4 Phase III, randomized, placebo controlled, parallel group, multicenter trials have been published that evaluate the efficacy of linaclotide in the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation.[4,6,11] All studies evaluated the clinical efficacy and safety of linaclotic in the treatment of CIC or IBS-C. Baseline demographic characteristics in the CIC trials were similar and well-matched; baseline demographics in the IBS-C trials were similar except for sex in trial MCP-103-302, which had a higher proportion of males in the placebo arm (p=0.038). Baseline clinical characteristics were simi in all trials with the exception of abdominal fullness (P=0.011), stool consistency (P=0.046) and straining (P=0.020) in IBS-C trial LIN-MD-31. Patients in all trials were predominantly white, female, under age 65, and with a mean age range of 43 to 49 years. Efficacy data was evaluated for all primary endpoints at 12 week based on intention-to-treat populations who reported at least one post-randomization, complete spontaneous bowel movement (CSBM). For all studies, patient were allowed to continue a stable, continuous regimen of fiber, bulk laxatives, or stool softeners if constant dose was maintained. Oral or suppository bisacodyl to 15 mg was allowed as rescue medication for severe constipation at 72 hrs after the last bowel movement or for intolerable constipation.

Of the phase III trials, two were fair quality trials that evaluated linaclotide vs. placebo in patients with CIC. Trials LIN-MD-**01** and MCP-103-**303** were identical, except for the inclusion of an additional 4-week randomized withdrawal after week 12 in trial 303.[6] Data for both trials were reported in the same publication, w a total of 1276 patients stratified post-randomization to receive 145 mcg linaclotide, 290 mcg linaclotide, or identical placebo once daily. Eligible patients include men and women ages 18 years or older with less than three spontaneous bowel movements (SBMs) per week plus one or more signs or symptoms during greate than 25% of bowel movements for a minimum of 12 weeks: straining; lumpy/hard stools; or sensation of incomplete evacuation. Patients must have also had les than or equal to six SBMs per week and less than three CSBMs during the baseline 14 weeks.

The primary efficacy endpoint for trials 01 and 303 was three or more CSBMs per week and an increase of one or more CSBMs from baseline during at least 9 ou of 12 weeks of treatment. This endpoint has been established as the FDA primary efficacy endpoint for CIC. It includes CSBM as a more clinically meaningful endpoint than spontaneous bowel movement, since constipation sufferers often complain about a sense of incomplete evacuation regardless of stool frequency.[6,12] The primary efficacy analysis was the difference in responder rate between linaclotide treatment arms and placebo. A total of 1272 patients reported at least one post-randomization CSBM and were included in the ITT analysis. There were statistically significant differences for all linaclotide doses compared to placebo, however the overall response rates that met the primary endpoint criteria were low for both studies. In trial 01, 16.0% of the 145 mcg arm and 21.3% of the 290 mcg arm attained the primary endpoint, compared to 6.0% of the placebo arm (NNT = 10 & 7, respectively; P≤0.01 & ≤0.001, respectively). trial 303, 21.2% of the 145 mcg arm and 19.4% of the 290 mcg arm vs. 3.3% of the placebo arm met the criteria for the primary endpoint (NNT=6 & 6, respective P≤0.001 for both linaclotide arms).

Secondary endpoint analyses for trials 01 and 303 revealed statistically significant differences for all endpoints, including stool frequency, stool consistency, severity of straining, abdominal discomfort, bloating, and constipation severity. The FDA considered the following secondary endpoints to be appropriate for inclusion in labeling: weekly change from baseline in number of CSBMs and SBMs, and change from baseline stool consistency based on the validated 7-point Bristol Stool Form Scale.[12] A score of 1 on the BSFS is indicative of constipation, while a score of 7 indicates diarrhea. For all linaclotide arms, CSBMs increased by approximately two per week compared to less than one for placebo, while SBMs increased by approximately three per week compared to an increase of one for placebo (all P-values <0.001). Overall, mean baseline stool consistency scores for all arms were approximately a 2 (lumpy, indicative of constipation). At 12 week

linaclotide arm mean scores increased to 4 (smooth, soft stool) vs. 3 (cracks, suggesting hardness) for placebo, all P-values <0.001. In regard to other secondary endpoints, the FDA determined in its summary review that the scoring systems used to assess observed treatment changes for severity of straining, abdominal discomfort, bloating, and constipation severity were problematic.[12] The ordinal scales utilized for these secondary endpoints were not validated. Patients were also asked to rate constipation symptoms compared to baseline, i.e. over an extended period of time & introducing the potential for recall bias. For example, weekly questions to evaluate bloating and abdominal discomfort were considered problematic because wording did not specify "severity" even though response options included "none, mild, moderate, severe, or very severe" on an ordinal scale of 1 to 5. In addition, mean and median baseline scores were in the range of on all arms (moderate), but only dropped to a range considered to be mild constipation for both linaclotide and placebo arms.

Two additional phase III trials have been published evaluating the efficacy of linaclotide. Trials LIN-MD-**31** and MCP-103-**302** were fair quality trials evaluating 29 mcg linaclotide vs. placebo in patients with IBS-C, with the same design methods for primary endpoint assessments.[4,11] Trial 31 included an additional 4-week randomized withdrawal period, while trial 302 gathered additional efficacy and safety data as tertiary analyses beyond the 12-week primary endpoint through 2 weeks. Eligible patients included men and women ages 18 years or older who met modified Rome II criteria for IBS-C, plus abdominal pain or discomfort with at least 2 of 3 features reported for a minimum of 12 weeks in the 12 months before screening: relieved w/defecation; onset associated with a change in the frequency of stool; or onset associated with a change in the form of stool before taking tegaserod or lubiprostone. Patients must also have had less than three SBMs per week and one or more signs or symptoms during greater than 25% of bowel movements for a minimum of 12 weeks: straining; lumpy/hard stools; a sensation of incomplete evacuation during greater than 25% of bowel movements, plus an average score of at least 3 for daily abdominal pain and an average of less than three CSBMs per week and less than or equal to five SBMs per week. Both trials included the same four primary efficacy endpoints assessed at 12 week

A total of 804 patients in trial 31 and 800 patients in trial 302 completed at least one post-randomization report and were evaluated in the ITT populations. Primary efficacy endpoints included: a) responders with at least a 30% reduction in abdominal pain and an increase of at least one CSBM from baseline in at leas out of 12 weeks (the FDA primary endpoint established for IBS-C),[12] b) at least a 30% reduction in the average daily worst abdominal pain for at least 9 out of 12 wks, c) at least three CSBMs and an increase of at least one CSBM from baseline for at least 9 out of 12 weeks, and 4) a combined responder (a+b). Similar to the CIC trials, the primary efficacy analysis was the difference in responder rate between linaclotide treatment arms and placebo. The percent response to treatmen by study is tabulated below. All results for trial 302 were statistically significant with P-values <0.0001; P-values for trial 31 were <0.0001, except for endpoint b (P=0.0262) and endpoint d (P=0.0004). Similar to the CIC trials, overall response rates to linaclotide were low even though results were statistically significant when compared to placebo.

Primary Efficacy Endpoints[4,11,12]	MCP-103-302		LIN-MD-31	
	Linaclotide 290 mcg (N=401)	Placebo (N=403)	Linaclotide 290 mcg (N=405)	Placebo (N=395)
6/12 Week APC +1 Responder[a]				
Responder %	33.7	13.9	33.6	21.0
NNT	5		8	
9/12 Week Abdominal Pain Responder[b]				
Responder %	38.9	19.6	34.3	27.1
NNT	5		14	
9/12 Week CSBM 3+1 Responder[c]				
Responder %	18.0	5.0	19.5	6.3
NNT	8		8	
9/12 Week APC 3+1 Responder[d]				
Responder %	12.7	3.0	12.1	5.1
NNT	10		14	

[a]FDA endpoint: ≥30% abdominal pain reduction and increase ≥1 CSBM fr baseline in the same week for ≥6/12 weeks.; [b]≥30% decrease in avg daily worst abdominal pain for 9/12 weeks; [c]≥3 CSBMs & an increas ≥1 CSBM from baseline for 9/12 weeks; [d]combined responder: decrease of ≥30% in avg daily worst abdominal pain score, ≥3 CSBMs, & ar increase of ≥1 CSBM from baseline in the same wk for ≥9/12 weeks.

Of note, in the IBS-C phase III trials the FDA defined primary endpoint was not as rigorous as the 9 out of 12 week "APC 3+1 responder". Responder rates trended down as the endpoint for the IBS-C trials became more rigorous. While primary endpoints were assessed at 12 weeks, differences in responder rates in trial 302 did remain statistically significant with a sustained effect at 26 weeks for linaclotide vs. placebo. Response rates in the linaclotide arm were 32.4%, 36.9%, 15.7%, 12.0% vs. 13.2%, 17.4%, 3.5%, 2.5% for placebo for primary endpoints a-d, respectively (P<0.0001 for all analyses; endpoints a-d defined in table above). For trial 302 primary endpoints, NNTs remained in a similar range of 5 to 11 at 26 weeks, compared to a range of 5 to 10 at 12 weeks.

A total of 10 secondary endpoints were analyzed in trials 31 and 302. However, the FDA expressed concerns with secondary endpoints similar to the CIC trials, specifically in regard to abdominal discomfort, bloating, and severity of straining.[12] Reviewers concluded that the following two secondary endpoints could be included in the narrative: 1) change from baseline in the 12-week CSBM frequency rate, and 2) change from baseline in week-12 abdominal pain. From baseline t 12 weeks, the difference in the CSBM frequency rate between linaclotide and placebo was approximately 1.5 CSBMs. For mean abdominal pain scores, the difference between linaclotide and placebo was approximately a decrease of 0.7 points on a scale of 0 to 10. In comparison to the CIC trials, mean scores for stoc consistency increased from approximately 2 to 4.3-4.5 for linaclotide treated arms, and from 2 to 3 for placebo arms.

Additional data regarding the efficacy of linaclotide for CIC and IBS-C is available from two phase II, multicenter, randomized, double blind, placebo-controlled dose-range finding trials evaluating the efficacy of linaclotide.[13,14] Primary endpoints did not match the defined endpoints of the phase III trials and were not included in the FDA's Summary Review. However, primary endpoints were similar to secondary endpoints from the phase III trials and provide additional efficacy data in regard to appropriate dosing regimens for linaclotide. Both trials evaluated four dosing regimens of linaclotide 75 µg, 150 µg, 300 µg, and 600 µg vs. placebo.

The phase IIa trial published by Lembo et al. evaluated linaclotide vs. placebo in an ITT population of 307 patients with chronic constipation.[13] The primary endpoint was the mean change from baseline to 4 weeks in weekly SBM rates. It is unclear if additional endpoints were established a priori or if additional

endpoints were considered secondary assessments. Similar to the phase III trials, ordinal scales used for severity assessments of additional endpoints were not validated. However, for the primary endpoint there was a linear dose response in the mean frequency of SBMs from baseline to 4 weeks, with increases of 2.6, 3.3, 3.6 and 4.3 SBMs for doses of 75, 150, 300, and 600 µg respectively, compared to 1.5 for placebo (P<0.05). There was also a trend toward improvement in mean weekly CSBM frequency and stool consistency with increasing dose; however, results should be interpreted with caution given that the description of additional endpoints is vague in regard to hierarchy and whether they were ad hoc analyses. While bowel function trended toward greatest improvement at the 600 µg dose, there were also more side effects reported at this dose, with diarrhea as the most common adverse event. Authors concluded that the 150 µg and 300 µg doses of linaclotide provided the best balance of efficacy and safety for patients with chronic constipation.

The phase IIb trial published by Johnston et al. evaluated linaclotide vs. placebo in an ITT population of 419 patients with IBS-C.[14] The primary endpoint was the mean change from baseline to 12 weeks in weekly CSBM rates. Similar to the phase IIa trial, it is unclear if a hierarchy of additional endpoints was established and ordinal scales for severity measures were not validated. Results for the primary endpoint across all arms were statistically significant (all P<0.01). Mean increases for CSBM frequency ranged from 2.5 to 3.6, with the largest increase of 3.6 CSBMs occurring in the 300 µg arm (P<0.001). Diarrhea was the only dose-dependent side effect. Authors concluded that the 300 µg dose provided comparable efficacy to the 600 µg dose with fewer GI side effects, and recommended the dose be selected for phase III studies.

To date, comparative efficacy data of linaclotide vs. commonly used laxatives is lacking. However, a recent systematic review and meta-analysis was published that provides some insight into how linaclotide compares to other therapies for chronic constipation.[8] Twenty-one randomized controlled trials were evaluated for the effectiveness of laxatives and pharmacological therapies in the treatment of CIC, including linaclotide. Authors concluded the following agents were more effective than placebo: linaclotide (RR 0.84; 95% CI 0.80-0.87); lubiprostone (RR 0.67; 95% CI 0.56-0.80); laxatives (RR 0.52; 95% CI 0.46-0.60; included PEG, sodium picosulfate and bisacodyl). Prucalopride was also found to be more effective than placebo (RR 0.82; 95% CI 0.76-0.88), but it is not available in the U.S. Numbers needed to treat to prevent one patient from failing to respond to therapy ranged from 3 to 6.

There are no published comparative efficacy trials comparing linaclotide to lubiprostone. However, overall response rates to lubiprostone vs. placebo in an adult female, IBS-C population in two double-blind, placebo controlled trials was 13.8/7.8% and 12.1/5.7%.[15] The primary endpoint for the lubiprostone IBS-C trials was based on the patient's response to a global symptom relief scale and was less rigorous than the endpoints in the linaclotide CIC/IBS-C trials. It is therefore difficult to interpret any differences in response rates to linaclotide vs. lubiprostone. Head-to-head trials are needed to evaluate the efficacy of linaclotide compared to other available agents for the treatment of chronic constipation.

In conclusion, the overall strength of evidence is moderate in support of linaclotide's efficacy in the treatment of CIC and IBS-C. However, statistically significant results may not be clinically meaningful to patients. Overall response rates to linaclotide are low, and the measures utilized to evaluate clinically relevant symptom reduction for abdominal pain and symptom severity were suboptimal in phase II and phase III trials. For phase III trial primary efficacy endpoints, a response to 9 out of 12 weeks in the case of CIC and to 6 out of 12 weeks for IBS-C means up to 50% of the time the patient may experience no relief from symptoms. In addition, the impact of linaclotide on health-related quality of life was not assessed as a pre-defined primary or secondary endpoint. Patients in the general population who have constipation may be older, since prevalence increases with age. The data may not accurately reflect any differences in response due to sex as the study populations were predominantly female. Finally, the FDA primary endpoints for IBS-C and CIC are relatively new and have not been fully vetted in clinical trials. Therefore, it is difficult to determine the clinical meaningfulness of the endpoints, e.g. with an increase of one CSBM per week over baseline the patient may still experience discomfort and/or pain if their baseline number of CSBMs was zero. Patients should still seek to optimize all other options for treating IBS-C and CIC before trying linaclotide.

Clinical Safety:

The safety of linaclotide in patients under the age of 18 has yet to be determined. There is a black box warning for patients up to 6 years of age and use is discouraged in pediatric patients 6 through 17 years of age. The FDA has requested that the manufacturer perform additional safety analyses in animal and human models to determine the safety profile for this population. This request follows data demonstrating toxicity in neonatal and juvenile mice. In addition, the FDA has expressed concern that the greatest safety risk of linaclotide is the theoretical development of anti-linaclotide antibodies and cross-reaction with endogenous peptides. No data is available to date to assess this risk; however the manufacturer is required to perform additional anti-drug antibody assays plus a clinical trial in adults to determine the risk of developing antibody responses in response to treatment.[1,12]

The most common adverse drug event in all four phase III trials was diarrhea, with an overall incidence of 16% at the 145 mcg dose of linaclotide and 20% at 290 mcg linaclotide.[12] Likewise, data from the phase II trials suggests a trend of increasing incidence of diarrhea with increased doses of linaclotide. Two open-label, long-term safety studies have since been conducted on linaclotide. Although published data is not available, the outcomes have been included in the FDA Summary Review.[12] Nearly a third of both CIC and IBS-C patients reported diarrhea as an adverse event. Overall, in the long-term studies diarrhea was reported as severe in 3% of patients. The agent carries a pregnancy rating of "C".

Seven known deaths occurred from all study populations, however none were attributed to the drug. One patient died during screening prior to study drug exposure, two patients died from cancer, one patient fell from a ladder, and three deaths were attributed to narcotic use. There was no evidence linking linaclotide to renal or hepatic toxicity, correlating to low systemic exposure to the drug. None of the data from the randomized controlled trials established a causal link between linaclotide and diverticulitis, gall bladder disease, ischemic colitis, or hematological disorders; however, there was a higher percentage of patients with low RBC levels in the 290 microgram arms of the IBS-C and CIC trials compared to placebo and the lower dose arm (0.5%/0.2%/0.2%, respectively). The meaning of this finding is unclear, as there was no statistical difference between HCT or Hgb between study arms.[12]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Reduced symptom severity or elimination of symptoms
   -Improved bowel function
   -Reduced pain/discomfort associated with disease state
2) Improved health-related quality of life
3) Tolerability

Primary Study Endpoints (Phase III Trials):

1) CIC trials: Patients with at least 3 CSBMs per week and an increase of at least one CSBM per wk from baseline for at least 9 weeks during the 12-week treatment period (FDA defined 1° endpoint)
2) IBS-C trials: Responders with ≥30% abdominal pain reduction and an increase of at least one CSBM from baseline in the same week for at least 6 out of 12 weeks (FDA defined 1° endpoint)
3) IBS-C trials: ≥30% reduction of average daily worst abdominal pain for at least 9 out of 12 wks
4) IBS-C trials: at least 3 CSBMs & an increase of at least one CSBM from baseline for 9 out of 12 weeks
5) IBS-C trials: Combined responder: decrease of ≥30% in avg daily worst abdominal pain score, ≥3 CSBMs, & an increase of ≥1 CSBM from baseline in the same wk for ≥9/12 weeks

Ref./Study Design	Drug Regimens/ Duration	Patient Population (R1/R2/P)	N	Outcomes/ Efficacy Results (CI, p-values)	NNT	Safety Results (CI, p-values)	NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
1. Lembo AJ, et al. [6] **Trial MCP-103-303 (CIC)** DB, PC, PG, MC, RCT Phase III	R1: Linaclotide 145 µg R2: Linaclotide 290 µg P: Placebo Duration: 12 weeks Trials 303 and 01 were identical, except Trial 303 had an additional 4-wk randomized withdrawal after 12 weeks.	Mean age: 47/48/49 years Male: 13/12/12.9% White: 72.7/75.6/76.6% Age ≥65 yrs: 12.4/12.5/13.4% Inclusion Criteria: Men & women ≥18 yrs with <3 SBMs/wk + one or more s/sx during >25% BMs for min of 12 weeks: straining; lumpy/hard stools; sensation of incomplete evacuation. Plus: ≤6 SBMs/wk & <3 CSBMs during baseline 14 wks. Exclusion Criteria: loose or watery stool in absence of laxative for >25% BMs in preceding 12 wks; mushy stool for >1 SBM during baseline, Rome II criteria for IBS; hx pelvic floor dysfunction; alarm sx confirmed by colonoscopy. Patients on a stable, continuous regimen of fiber, bulk laxatives, or stool softeners allowed to continue if constant dose was maintained. PO or suppository bisacodyl up to 15 mg/day allowed as rescue medication for severe constipation at 72 hrs after last BM or for intolerable constipation.	N=643 ITT = 642 R1: 217 R2: 216 P: 209	FDA 1° endpoints: Patients with ≥ 3 CSBMs/week and an ↑ of at least one CSBM/wk from baseline for ≥ 9 weeks during the 12-wk treatment period [n (%)]: R1: 46 (21.2); P≤0.001 R2: 42 (19.4); P≤0.001 P: 7(3.3) OR (linaclotide: Placebo): R1: 7.72, 95% CI (3.41,17.47) P≤0.0001 R2: 7.21, 95% CI (3.14,16.59) P≤0.0001 2° endpoints: CSBMs change from baseline (no./wk): R1: 1.9 R2: 2.0 P: 0.5 P<0.001 SBMs change from baseline (no./wk): R1: 3.0 R2: 3.0 P: 1.1 P<0.001 Stool consistency, change from baseline score: R1: 1.9 R2: 1.8 P: 0.6 P<0.001	NNT R1: 6 R2: 6	**Pooled data 303/01** (R1/R2/P; CI & P-values not reported): Any events: 60.5%/55.7%/52.1% The most common dose-related ADE (%): Diarrhea: 16/14.2/4.7 Other ADEs in ≥3% of patients: flatulence, ab pain, URI, ab distention, nasopharyngitis, sinusitis, upper ab pain Mortality: 0% (one pt died from fentanyl OD) Serious ADEs (%): 1.4/2.6/2.1 Discontinuation due to ADEs (%): 7.9/7.3/4.2 1st occurrence of diarrhea ADE reported in 1st 2 weeks: 61.7% Diarrhea graded as severe ADE (R/P; %): 1.5/0.2	NNH R1: 9 R2: 10	**Quality Rating:** Fair **Analysis:** ITT; total of 1272 patients (trials 01 & 303); 4 patients out of 1276 did not report any post-randomization CSBMs. Sensitivity analyses including the 4 non-reporting patients revealed similar results. Observed-cases approach to missing post-baseline data with last-observation-carried-forward applied. **Overall Attrition:** R1/R2/P (%) 14.3/18.4/15.3 **Risk of Bias** **Internal Validity:** Selection: Low bias; randomization and allocation concealment clear; via offsite IVRS Performance: Low bias, blinding of patients and study monitors; unclear how PK samples at wk 7 were blinded but linaclotide levels were not detectable Attrition: Low bias; Less than 20% overall, with <10% difference between treatment groups. Adherence to IVRS: 88.3% Level of adherence to study medication, crossovers, and contamination not discussed. **External Validity:** Patient Characteristics: similar between groups; may not reflect general population Setting: geographic region used as a fixed effect term for analysis instead of trial center as some sites had small numbers of patients Outcomes: 200 patients provided 90% power to detect treatment differences in the primary endpoint. 2°outcomes that required pts to recall current symptoms compared to baseline subject to bias (e.g., severity, straining).

2. Lembo AJ, et al. [6] **Trial LIN-MD-01 (CIC)** DB, PC, PG, MC, RCT Phase III	R1: Linaclotide 145 µg R2: Linaclotide 290 µg P: Placebo Duration: 12 weeks Trials 303 and 01 were identical, except Trial 303 had an additional 4-wk randomized withdrawal after 12 weeks.	Mean age: 49/47/47 years Male: 8.5/11.4/8.8% White: 78.9/75.2/78.1% Age ≥65 yrs: 11.3/10.4/12.6% Same inclusion/exclusion criteria as Trial 303	N=633 ITT= 630 R1: 213 R2: 202 P: 215	FDA 1° endpoints: Patients with ≥ 3 CSBMs/week and an ↑ of at least one CSBM/wk from baseline for ≥ 9 weeks during the 12-wk treatment period [n (%)]: R1: 34 (16.0); P≤0.01 R2: 43 (21.3); P≤0.001 P: 13(6.0) OR (linaclotide: Placebo): R1: 2.93 95% CI (1.50,5.72) P≤0.0012 R2: 4.22 95% CI (2.20,8.10) P≤0.0001 2° endpoints: CSBMs change from baseline (no./wk): R1: 2.0 R2: 2.7 P: 0.6 P <0.001 SBMs change from baseline (no./wk): R1: 3.4 R2: 3.7 P: 1.1 P <0.001 Stool consistency, change from baseline score: R1: 1.8 R2: 2.0 P: 0.6 P<0.001	NNT R1: 10 R2: 7	**Pooled data 303/01** (R1/R2/P CI & p-values not reported)**:** ADEs, any events (%): 60.5/55.7/52.1 The most common dose-related ADE (%): Diarrhea: 16/14.2/4.7 Other ADEs in ≥3% of patients flatulence, URI, ab pain, ab distention, nasopharyngitis, sinusitis, upper ab pain Mortality: 0% (one pt died from fentanyl OD) Serious ADEs (%): 1.4/2.6/2.1 Discontinuation due to ADEs (%): 7.9/7.3/4.2 1st occurrence of diarrhea ADE reported in 1st 2 weeks: 61.7% Diarrhea graded as severe ADE (R/P; %): 1.5/0.2	NNH R1: 9 R2: 10	**Quality Rating:** Fair **Analysis:** ITT; total of 1272 patients (trials 01 & 303); 4 patients out of 1276 did not report any post-randomization CSBMs. Sensitivity analyses including 4 non-reporting patients revealed similar results. Observed-cases approach to missing post-baseline data with last-observation-carried-forward applied. **Overall Attrition:** R1/R2/P (%) 18.8/17.6/11.1 **Risk of Bias** **Internal Validity:** Selection: Low bias; computerized randomization and allocation concealment via offsite IVRS Performance: Low bias, blinding of patients and study monitors; unclear how PK samples at wk 7 were blinded but linaclotide levels were not detectable Attrition: Low bias; Less than 20% overall, with <10% difference between treatment groups. Adherence to IVRS: 86.3% Level of adherence to study medication, crossovers and contamination not discussed **External Validity:** Patient Characteristics: similar between groups; may not reflect general population Setting: geographic region used as a fixed effect term for analysis instead of trial center as some sites had small numbers of patients Outcomes: 200 patients provided 90% power to detect treatment differences in the primary endpoint. 2°outcomes that required pts to recall current symptoms compared to baseline subject to bias (e.g., severity, straining)

3. Rao S, et al.[4] **Trial LIN-MD-31** (IBS-C) DB, PC, PG, MC, RCT Phase III	R: Linaclotide 290 µg P: Placebo Duration: 12 weeks + 4 weeks RW period	Mean age: 43.3/43.7 years Male: 9.4/9.6% White: 77.5/76.2% Age ≥65 yrs: 4.7/6.6% Inclusion Criteria: Men and women ≥ 18 yrs who met modified Rome II criteria fo IBS-C; abdominal pain or discomfort with ≥ 2 of 3 features reported for min o 12 wks in the 12 mo before screening: i) relieved w/defecation, ii) onset assoc w/Δ freq of stool, or iii) onset assoc w/ Δ in form of stool before taking tegaserod or lubiprostone; < 3 SBMs/wk + one or more s/sx during >25% BMs for min of 12 weeks: straining; lumpy/hard stools; sensation of incomplete evacuation; avg score of ≥3 for daily ab pain; avg <3 CSBMs/wk and ≤5 SBMs/wk. Exclusion Criteria: loose or watery stool for >25% BMs in preceeding12 wks; durin baseline, a BSFS score of 7 for any SBM, or 6 for >1 SBM; hx cathartic colon, laxative abuse, ischemic colitis, GI surgery, diverticulitis, family hx colorectal ca. Constipating drugs like narcotics excluded; however, patients on stable doses of drugs for IBS for 3 days prior to trial that may cause constipation allowed to continue (e.g. TCAs). Rescue med allowed ~ CIC trials	N= 803 ITT: 800 R: 405 P: 395	<u>1° endpoints (n (%))</u> a) Responders with ≥30% ↓ ab pain and ↑ ≥ 1 CSBM from baseline in ≥ 6/12 wks (FDA 1°): R: 136 (33.6) P: 83 (21.0) OR (95% CI): 1.9 (1.4,2.7) P<0.0001 b) ≥30% ↓ avg daily worst ab pain (9/12 wks) R: 139 (34.3) P: 107 (27.1) OR (95% CI): 1.4 (1.0,1.9) P=0.0262 c) ≥3 CSBMs & ≥1 CSBM from baseline (≥9/12 weeks) R: 79 (19.5) P: 25 (6.3) OR (95% CI): 3.7 (2.3,5.9) P<0.0001 d) Combined responder (a+b): R: 49 (12.1) P: 20 (5.1) OR (95% CI): 2.6 (1.5,4.5) P=0.0004 <u>2° endpoints</u> a) CSBM Δ from baseline (mean): R: 2.3 P: 0.7 P<0.0001 b) Worst ab pain, Δ from baseline (mean): R: -1.9 P: -1.1 P<0.0001	NNT (<u>1°</u>) a) 8 b) 14 c) 8 d) 14 <u>NNT (2°)</u> N/A	ADEs, any events (%): 56.2/53.0 ADEs with ≥2% incidence (%): Diarrhea: 19.5/3.5 P<0.0001 Abdominal pain: 5.4/2.5; P=0.0462 Flatulence: 4.9/1.5; P=0.0084 Headache: 4.9/3.5; P=0.3825 Abdominal distension: 2.2/0.8; P=0.1434 Mortality: No deaths during treatment SAEs: 2 patients each arm (0.5% both arms) Discontinuation due to ADEs (%): 7.9/2.8 Discontinuation due to diarrhea (%): 5.7/0.3 >50% of patients w/diarrhea experienced in the 1st 2 week No diarrhea graded as severe ADE	NNH R: 6	**Quality Rating:** Fair **Analysis:** ITT; 800 patients met criteria for efficacy analysis & 802 met criteria for safety analysis **Overall Attrition:** (R/P): 23.2%/15.6% **<u>Risk of Bias</u>** **Internal Validity:** <u>Selection:</u> Low bias; computerized randomization and allocation concealment via offsite IVRS <u>Performance:</u> Low bias, blinding of patients and study monitors; unclear how PK samples at baseline and wk 4 were blinded but linaclotide levels were not detectable <u>Attrition (R/P):</u> Potential bias; overall attrition of linaclotide arm >20% due to greater loss to follow-up (4.2/2.5%) & incidence of adverse events (7.9/2.5%). Between group difference <10%. <u>Adherence to IVRS:</u> (R:P; %): 71/73 Level of adherence to study medication, crossovers and contamination not discussed. **External Validity:** <u>Patient Characteristics</u>: significant differences existed at baseline for symptoms of abdominal fullness, stool consistency & straining; may not reflect general population. <u>Setting:</u> geographic region used as a fixed effect term for analysis instead of trial center as some sites had small numbers of patients <u>Outcomes:</u> 400 patients per arm provided >85% power to detect treatment differences. Comorbid conditions such as diverticulitis may be present in the general population; Patients could meet some criteria for primary endpoints but still have dx of constipation according to Rome III guidelines (if <3 BMs/wk).

4. Chey WD, et al.[11] **Trial MCP-103-302** (IBS-C) DB, PC, PG, MC, RCT Phase III	R: Linaclotide 290 µg P: Placebo Duration: 26 weeks 1° and 2° efficacy assessed at 12 weeks Safety data assessed at 26 weeks	Mean age: 44.6/44.0 years Male: 8.2/12.7% White: 78.8/77.2% Age ≥65 yrs: 5.7/4.2% Inclusion Criteria: Men and women ≥ 18 yrs who met modified Rome II criteria for IBS-C; abdominal pain or discomfort with ≥ 2 of 3 features reported for min of 12 wks in the 12 mo before screening: i) relieved w/defecation, ii) onset assoc w/Δ freq of stool, or iii) onset assoc w/ Δ in form of stool before taking tegaserod or lubiprostone; < 3 SBMs/wk + one or more s/sx during >25% BMs for min of 12 weeks: straining; lumpy/hard stools; sensation of incomplete evacuation; avg score of ≥3 for daily ab pain; avg <3 CSBMs/wk and ≤5 SBMs/wk. Exclusion Criteria: loose or watery stool in absence of laxative for >25% BMs in preceding 12 wks; mushy stool for >1 SBM or watery stool for any SBM during baseline; hx GI resection, cholecystectomy 2 mo or ab surgery 6 mo before trial, bariatric surgery; hx diverticulitis. Constipating drugs like narcotics excluded; however, patients on stable doses of drugs for IBS for 30 days prior to trial that may cause constipation allowed to continue (e.g. TCAs).	N=805 ITT=804 R: 401 P: 403	1° endpoints (P<0.0001 all endpoints) a) % responders with ≥30% ↓ ab pain and ↑ ≥ 1 CSBM from baseline in ≥ 6/12 wks (FDA 1°): R: 33.7% P: 13.9% OR (95% CI): 3.2 (2.2, 4.5) b) ≥30% ↓ avg daily worst ab pain (9/12 wks) R: 38.9% P: 19.6% OR (95% CI): 2.6 (1.9, 3.6) c) ≥3 CSBMs & ≥1 CSBM from baseline (≥9/12 weeks) R: 18% P: 5.0% OR (95% CI): 4.2 (2.5, 7.0) d) Combined responder (a+b): R: 12.7% P: 3.0% OR (95% CI): 4.7 (2.4,8.8) 2° endpoints a) CSBM Δ from baseline (mean): R: 2.2 P: 0.7 b) Worst ab pain, Δ from baseline (mean): R: -1.9 P: -1.1	NNT (1°) a) 5 b) 5 c) 8 d) 10 NNT(2°) N/A	ADEs, any events (%): R: 65.4% P: 56.6% P<0.05 ADEs with ≥2% incidence (%): Diarrhea: 19.7/2.5 P<0.0001 No other statistically significant differences in ADEs between treatment groups Mortality: 0% SAEs: R: 1% P: 1.7% (none related to linaclotide) Discontinuation due to ADEs (%): 10.2%/2.5% Discontinuation due to diarrhea (%): 4.5%/0.2% Onset of diarrhea in linaclotide-treated patients: Within 1 wk: 48.1% Within 4 wks: 75.9% No diarrhea graded as severe ADE	NNH R: 6	**Quality Rating:** Fair **Analysis:** ITT; 804 patients met criteria for analysis. **Risk of Bias** **Internal Validity:** Selection: Low bias; computerized randomization via IVRS Performance: Potential bias; blinding of patients and study monitors; unclear how PK samples at baseline and wk 4 were blinded. Out of 98 patients analyzed, 2 had levels of linaclotide just above threshold of 0.2 ng/ml. Attrition: Potential bias; only reported for 26, not 12 weeks; R=26.9%/P=24.3%; between group differences was 2.6% Adherence: Performed by pill counts at visits up to 12 weeks; 94/95% (R:P) **External Validity:** Patient Characteristics: no significant differences between treatment groups except for sex, with a higher percentage of females in the linaclotide arm (P=0.038); may not reflect general population Setting: geographic region used as a fixed effect term for analysis instead of trial center as some sites had small numbers of patients Outcomes: 400 patients per arm provided >85% power to detect treatment differences. Comorbid conditions such as diverticulitis may be present in the general population; Patients could meet some criteria for primary endpoints but still have a dx of constipation according to Rome III guidelines (if <3 BMs/wk)

5. Johnston JM, et al.[14] Linaclotide Improves Abdominal Pain & Bowel Habits in a Phase IIb Study of Patients with IBS-C DB, PC, MC, RCT Phase IIb dose-range finding study	R1: Linaclotide 75 µg R2: Linaclotide 150 µg R3: Linaclotide 300 µg R4: Linaclotide 600 µg P: Placebo	Mean Age (range): 44.4 (18-72) yrs Male: 8% White: 80% Inclusion Criteria: men and women ≥ 18 yrs who met modified Rome II criteria for IBS reporting <3 SBMs per week & 1 or more of the following Sx for ≥ 12 weeks in the 12 months preceding study entry: 1) straining during ≥ 25% of BMs; 2) lumpy/hard stools during ≥ 25% of BMs; 3) sensation of incomplete evacuation during >25% of BMs. During 2-wk baseline, required to report a mean score of ≥ 2.0 for daily assessment of ab pain or ab discomfort, plus mean of <3 CSBMs and ≤6 SBMs/week. Exclusion criteria: pregnant or breast-feeding patients, presence of loose, mushy, watery stools for >25% BMs OR score of 6 or 7 on BSFS w/o laxative use for previous 24 hrs during 2-wk baseline, Hx of pelvic floor dysfunction, colon surgery, ab surgery in previous 60 days, need for manual maneuvers for BM, or laxative abuse. PO or suppository bisacodyl up to 15 mg/day allowed as rescue medication for severe constipation at 72 hrs after last BM, provided no >2 doses and none used 3 days before first dose study med. Stable, continuous fiber regimen & antidepressants allowed if stable 30 days prior to enrollment.	N = 420 ITT = 419 R1: 79 R2: 82 R3: 84 R4: 89 P: 85	<u>1° endpoint:</u> Mean change from baseline to 12 weeks in weekly CSBM rate: R1: 2.90 (P<0.001) R2: 2.49 (P<0.01) R3: 3.61 (P<0.001) R4: 2.68 (P<0.001) P: 1.01 <u>Additional endpoints:</u> CSBM 75% responder (≥ 3 CSBMs/week and an ↑ of ≥1 CSBM/wk for ≥ 9 out of 12 weeks). for all values except linaclotide 150 µg : R1: 25.3% (P<0.05) R2: 19.5% R3: 32.1% (P<0.01) R4: 23.6% (P<0.05) P: 11.8% Mean change from baseline to 12 weeks in weekly SBM rate: R1: 4.62 (P<0.001) R2: 4.36 (P<0.001) R3: 4.97 (P<0.001) R4: 5.64 (P<0.001) P: 1.68 SBM 75% responder (≥ 3 SBMs/week and an ↑ of ≥1 SBM/wk for ≥ 9 out of 12 weeks) (%): R1: 54.4% (P<0.01) R2: 39.0% R3: 65.5% (P<0.001) R4: 52.8% (P<0.01) P: 29.4% Stool Consistency (BSFS mean change from baseline) R1: 1.91 (P<0.001) R2: 1.80 (P<0.001) R3: 2.28 (P<0.001) R4: 2.20 (P<0.001) P: 0.56	<u>NNT (1°)</u> N/A <u>NNT (2°)</u> R1: 7 R2: 13 R3: 5 R4: 8 N/A R1: 4 R2: 10 R3: 3 R4: 4 N/A	ADEs with ≥3% incidence (%): Diarrhea: 14.6% Abdominal pain: 5.4% UTI: 4.2% Nausea: 3.9% Nasopharyngitis: 3.3% Headache: 3.3% URTI: 3.3% Diarrhea was the only dose-dependent AE: R1:11.4% R2: 12.2% R3: 16.5% R4: 18.0% P: 1.2% Diarrhea graded as severe: R1: 2.3% R2: 2.5% R3: 1.2% R4: 4.5% Discontinuation due to AE (%) R1: 5% R2: 7.3% R3: 3.5% R4: 11.2% P: 2.3% Discontinuation due to diarrhea: R1: 2.5% R2: 4.9% R3: 1.1% R4: 6.7% P: 0% Median no. of days to initial onset of diarrhea: 4 Mortality: none reported	<u>NNH</u> R1: 10 R2: 9 R3: 7 R4:6	**Quality Rating:** Fair **Analysis:** ITT, 419 met criteria for analysis; missing data not imputed; analysis did not include a last observation carried forward approach (patients were considered non-responders for weeks with missing data) **Overall Attrition (R1/R2/R3/R4/P):** 20.2/18.3/16.5/20.2/23.5% Endpoints were not identified as a priori; it is unclear when additional endpoints were assessed P-values and confidence intervals not provided for safety data **<u>Risk of Bias</u>** **Internal Validity:** <u>Selection:</u> Low bias; computerized randomization via a statistician not associated with the trial <u>Performance:</u> Likely low bias; all study personnel blinded but a formal description of dummy placebo design was not provided <u>Attrition:</u> Potential bias; over 20% in 75 µg and 600 µg arms (R1 & R4) and placebo arms, however between group differences are < 10% <u>Adherence:</u> Patients reported time study medication (and any rescue medication) was taken daily via IVRS. Adherence rates not reported. **External Validity:** <u>Patient Characteristics:</u> No baseline P-values are provided; characteristics appear similar between treatment groups. Results may not reflect response in general population w/respect to race. <u>Setting:</u> U.S. geographic region used as a fixed effect term for analysis instead of trial center as some sites had small numbers of patients <u>Outcomes:</u> 80 patients per arm provided 95% power to detect treatment differences. Abdominal pain is a significant component of IBS, however the ordinal scale used to measure patient response to treatment was not validated. It is unclear which additional outcomes were identified a priori, therefore responses to non-validated instruments (mean changes in ab pain, bloating, straining) must be interpreted with caution when considering the general population.

6. Lembo AJ, et al.[13] Efficacy of Linaclotide for Patients with Chronic Constipation DB, PC, PG, MC, RCT Phase IIa dose-range finding study	R1: Linaclotide 75 µg R2: Linaclotide 150 µg R3: Linaclotide 300 µg R4: Linaclotide 600 µg P: Placebo	Mean Age (SD): 47.3 (13.7) yrs Male: 8% White: 84% Inclusion criteria: men and women ≥ 18 yrs who met modified Rome II criteria for CC reporting <3 SBMs per week & 1 or more of th following Sx for ≥ 12 weeks in the 12 months preceding study entry: 1) straining during > 25% of BMs; 2) lumpy/hard stools during > 25% of BMs; 3) sensation o incomplete evacuation during >25% of BMs. During 2-wk baseline, required to report avg <3 CSBMs and ≤ 6 SBMs per week via IVRS. Exclusion criteria: pregnant or breast-feeding patients, meeting Rome II criteria for IBS, hx pelvic floor dysfunction, need for manual maneuvers for BM, hx any colon surgery or ab operations within 60 days o study, hx laxative abuse. Score of 6 or 7 on BSFS excluded. PO or suppository bisacody up to 15 mg/day allowed as rescue medication for severe constipation at 72 hrs after last BM, provided no >2 doses and none used 3 days before first dose study med. Stable, continuous fiber regimen & antidepressants allowed if stable 30 days prior to enrollment.	N=310 ITT=307 R1:59 R2: 56 R3 62 R4: 62 P: 68	<u>1° endpoint:</u> Change in mean weekly SBM frequency from baseline to 4 weeks: R1: 2.6 R2:3.3 R3: 3.6 R4: 4.3 P:1.5 All P-values ≤0.05; test for linear trend was significant P<0.0001 <u>Additional endpoints</u> SBM responder rate (defined as weekly SBM rate ≥3 and a increase ≥1 relative to baseline): R1: 59.3% R2: 55.4% R3: 61.3% R4: 67.7% P: 32.4% All P-values ≤0.01 Change in mean weekly CSBM frequency from baseline to 4 weeks: R1: 1.5 R2: 1.6 R3:1.8 R4: 2.3 P: 0.5 All P-values ≤0.01 Change in overall PAC-QOL score from baseline to 4 weeks: R1: -0.72 (42.4%); P≤0.05 R2: -0.80 (44.6%); P≤0.05 R3: -0.67 (30.6%); P=0.0515 R4: -0.83 (48.4%); P≤0.05 P: -0.41 (26.5%)	<u>NNT (1°)</u> N/A R1: 4 R2: 4 R3: 3 R4: 3 N/A R1: 6 R2: 6 R3: 24 R4: 5	ADEs, patients with at least one event (n(%)): R1: 21 (35.6) R2: 18 (32.1) R3: 18 (29.0) R4:24 (38.1) P: 22 (31.9) Most common ADE was diarrhea (n(%)): R1: 3 (5.1%) R2: 5 (8.9%) R3: 3 (4.8%) R4: 9 (14.3%) P: 2 (2.9%) 2 incidences of diarrhea graded as severe, both in 600 µg arm Discontinuation due to ADE/diarrhea (n): R1: 0 R2: 2/1 R3: 2/2 R4: 3/3 P: 2 Half of reports of diarrhea were within 2 days of starting study medication Mortality: none reported P-values and confidence intervals not provided for safety data	<u>NNH</u> R1: 27 R2: 5 R3:-34 R4: 16 R1: 45 R2: 17 R3: 53 R4: 9	**Quality Rating:** Fair **Analysis:** ITT, 307 met criteria for analysis; observed cases approach to missing data applied (missing values not imputed) **Overall Attrition (R1/R2/R3/R4/P):** 8.5/10.5/6.5/19.0/11.6% Endpoints were not identified as a priori; it is unclear when additional endpoints were assessed **<u>Risk of Bias</u>** **Internal Validity:** <u>Selection:</u> Low bias; computerized randomization via validated computer system <u>Performance:</u> Likely low bias; all study personnel blinded but a formal description of dummy placebo design was not provided <u>Attrition:</u> Potential bias; <20% in all arms, however between group differences are >10% between R1 and placebo arms <u>Adherence:</u> Patients reported time study medication was taken daily via IVRS **External Validity:** <u>Patient Characteristics:</u> No baseline P-values are provided; more patients enrolled in placebo group; characteristics appear similar between treatment groups. Results may not reflect response general population w/respect to race or age. <u>Setting:</u> U.S. geographic region and treatment group used as fixed effect terms for analysis of covariance instead of trial center since trial was conducted at 57 clinical centers <u>Outcomes:</u> 60 patients per arm projected to provide 88% power to detect treatment differences (anticipating 10 patients lost per arm), however R4 600 µg arm lost 12 patients. Additional endpoints relied on non-validated instruments (mean changes in ab pain, constipation severity, bloating, straining and global relief); therefore results must be interpreted with caution. Primary endpoint has become more rigorous for recent phase III trials.

Study design abbreviations: DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel-group, MC=multi-center.
Results abbreviations: OR= Odds Ratio, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
Quality Rating: Good- likely valid; Fair- likely valid/possibly valid; Poor- fatal flaw-not valid

Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY[1]

Linaclotide is structurally related to endogenous guanylin peptides and acts as a guanylate cyclase-C (GC-C) agonist. Guanylate cyclase-C is present on the luminal surface of intestinal epithelium. Linaclotide and its active metabolite bind to GC-C and stimulate increases in intracellular and extracellular cyclic guanosine monophosphate (cGMP). Within intestinal epithelial cells, increases in cGMP initiate a signal-transduction cascade that activates the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel. This results in secretion of chloride and bicarbonate ions into the intestinal lumen, which ultimately results in increased intestinal fluid and accelerated intestinal transit. Linaclotide mediated increase in cGMP is thought to be the mechanism that leads to a reduction in intestinal pain symptoms, since increased cGMP has been shown to decrease the activity of pain-sensing nerves in animal models.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	Low systemic bioavailability; below the limit of quantitation with 145 mcg and 290 mcg doses
Protein Binding	Plasma concentrations following PO doses are not measurable, therefore degree of binding cannot be calculated
Elimination	Eliminated in feces. Recovery in stool averages 5% (fasted) and 3% (fed), virtually all as active metabolite.
Half-Life	Standard PK parameters cannot be calculated
Metabolism	Metabolized by the GI tract to active metabolite MM 419447 that lacks the tyrosine moiety. Drug and metabolite are proteolytically degraded in the lumen to smaller peptides and amino acids.

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
145 mcg 290 mcg	Oral	Once daily	IBS-C: 290 mcg CIC: 145 mcg (capsules)	Not required	Not required	**BBW** Safety & efficacy not established	Insufficient data to determine if dosage changes are warranted	Take on an empty stomach 30 minutes prior to first meal of the c Swallow capsules whole; do not break apart or chew

ALLERGIES/INTERACTIONS[1]

Systemic drug-drug interactions and/or plasma protein binding-mediated drug interactions are not anticipated due to the fact that linaclotide and its active metabolite are not measurable in plasma following oral administration. In vitro analysis indicates that the agent does not interact with the cytochrome P450 system; likewise, linaclotide is neither an inhibitor nor a substrate of P-glycoprotein. No severe allergic reactions occurred in the pooled phase 3 trial dataset however incidences of skin and respiratory symptoms suggestive of hypersensitivity were reported in both linaclotide and placebo treatment arms. The overal incidence of skin manifestations was 1.3% for linaclotide and 1.6% for placebo; the incidence of pulmonary manifestations of hypersensitivity was 0.7% fo linaclotide-treated patients and 0.5% in placebo-treated patients.

DRUG SAFETY[1,12]

Serious (REMS, Black Box Warnings, Contraindications):

- BBW: Contraindicated in pediatric patients up to 6 years of age. Avoid use in pediatric patients 6 through 17 years of age. Linaclotide has caused deaths i young juvenile mice at clinically relevant adult doses. The FDA has waived the requirement to study linaclotide in pediatric populations pending furthe studies to isolate the underlying cause of death in young mice.
- Contraindications: Pediatric patients up to age six; patients with mechanical gastrointestinal obstruction.
- Warnings and Precautions: Hold or stop the agent if severe diarrhea occurs. Suspected adverse reactions should be reported to 1-800-FDA-1088 o www.fda.gov/medwatch.
- REMS: not required as of October, 2012.

  The FDA has expressed concern that the greatest safety risk of linaclotide is the theoretical development of anti-linaclotide antibodies and cross-reactio with endogenous peptides. Such cross-reactivity could lead to deficiency syndromes. Reviewers concluded that likely adverse events could includ hypernatremia, volume overload, hypertension, and constipation. The FDA has indicated that anti-drug antibody assays must be developed and a clinica trial must be performed in adults to assess anti-drug antibody responses in patient samples.[12]

Look-alike / Sound-alike (LA/SA) Error Risk Potential: none identified.

Pregnancy/Lactation rating: Pregnancy rating of "C". No adequate, well-controlled studies of linaclotide have been performed in pregnant women. Fetal affects have been observed in animal studies at doses much higher than the 290 mcg ceiling dose, but only with maternal toxicity. Therefore, linaclotide should be used in pregnancy only when the benefit outweighs the risk. It is unknown whether linaclotide is excreted in human breast milk, however plasma levels of linaclotide and its metabolite are not measurable at approved doses. Caution is warranted when the agent is administered to nursing women.

Tolerability: Diarrhea was the most common adverse reaction reported in IBS-C and CIC patients. Severe diarrhea occurred at a rate of 2% for patients treated w both the 145 mcg and 290 mcg doses of linaclotide, vs. less than 1% of placebo-treated patients. Overall, 5% of linaclotide-treated patients discontinued due to diarrhea vs. less than 1% of placebo-treated patients. Diarrhea occurred in the first two weeks of treatment for the majority of patients treated with linaclotide. 8% of CIC patients treated with linaclotide and 4% of placebo-treated patients discontinued treatment prematurely due to adverse reactions.

ADVERSE REACTIONS[1]

IBS-C (Trials MCP-103-302 & LIN-MD-31; incidence ≥ 2.0% and greater than placebo)

Adverse Reactions	**Linaclotide 290 mcg [N=807] %**	**Placebo [N=798] %**
Gastrointestinal		
Diarrhea	20	3
Abdominal pain (any region)	7	5
Flatulence	4	2
Abdominal distention	2	1
Infections and Infestations		
Viral Gastroenteritis	3	1
Nervous System Disorders		
Headache	4	3

CIC (Trials LIN-MD-31 and MCP-103-302; incidence ≥ 2.0% and greater than placebo)

Adverse Reactions	Linaclotide 145 mcg [N=430] %	Placebo [N=423] %
Gastrointestinal		
Diarrhea	16	5
Abdominal pain (any region)	7	6
Flatulence	6	5
Abdominal distention	3	2
Infections and Infestations		
Upper respiratory tract infection	5	4
Sinusitis	3	2

References

1. Linzess. Prescribing Information. Forest Pharmaceuticals. St.Louis, MO, August 2012. Available online at: http://www.frx.com/pi/linzess_pi.pdf. Accessed October 16, 2012.
2. Rome Foundation, Inc. Appendix A: Rome III diagnostic criteria for functional gastrointestinal disorders. Last modified June 2, 2006. PDF available online at www.romecriteria.org/criteria. Accessed October 16, 2012.
3. Wald A. Clinical manifestations and diagnosis of irritable bowel syndrome. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2012. Topic last updated July 23, 2012. Accessed October 18, 2012.
4. Rao S, 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; September: 1-11. [epub ahead of print]
5. Lexi-Comp, Inc. (Lexi-Drugs TM). Lubiprostone: drug information. Lexi-Comp, Inc.; Copyright 2012 for handheld. Last updated October 19, 2012. Accessed October 19, 2012.
6. Lembo AJ, et al. Two randomized trials of linaclotide for chronic constipation. NEJM. 2011; 365; 527-36.
7. Wald A. Etiology and evaluation of chronic constipation in adults. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2012. Topic last updated August 22, 2012. Accessed October 18, 2012.
8. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. Gut. 2011;60:209-218.
9. NICE Technology Appraisal Guidance. Prucalopride for the treatment of chronic constipation in women. Review available online at http://publications.nice.org.uk/prucalopride-for-the-treatment-of-chronic-constipation-in-women-ta211/guidance. Issued December, 2010. Accessed November 6, 2012.
10. Ramkumar D, Rao S. Efficacy and safety of traditional medical therapies for chronic constipation: systematic review. Am J Gastroenterol. 2005;100:936-971.
11. Chey WD, 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; July: 1-11. [epub ahead of print]
12. Linzess, FDA Center for Drug Evaluation and Research. Summary Review. Published August 29, 2012. PDF available online at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202811Orig1s000SumR.pdf. Accessed October 16, 2012.
13. Lembo AJ, et al. Efficacy of linaclotide for patients with chronic constipation. Gastroenterology. 2010;138:886-895.
14. 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;139:1877-1886.
15. Amitiza. Prescribing Information. Sucampo Pharmaceuticals, Inc. Bethesda, MD, February 2011. Available online at http://www.amitiza.com/default.aspx. Accessed November 2, 2012.