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

BACKGROUND:

- Many people suffer from IBS and a portion of those suffer from IBS-Constipation. There are only a few medications for patients with IBS-C to help alleviate their abdominal pain and constipation.
- Linaclotide was proven efficacious in patients with chronic constipation.

OBJECTIVE:

- To determine the efficacy and safety of linaclotide in patients with irritable bowel syndrome with constipation (IBS-C).

METHODS

- Design: 12 week (with 4 week randomized withdrawal period), multi-center, randomized, double-blind, parallel-group, placebo-controlled trial.
- Inclusion: Patients who met modified Rome 2 criteria for IBS, abdominal pain (>3 daily pain score), or abdominal discomfort that had ≥2 of these three features: (i) relieved with defecation, (ii) onset associated with a change in frequency of stool, and (iii) onset associated with a change in form (appearance) of stool, or < 5 complete spontaneous bowel movements (CSBMs) for at least 12 weeks, which need not be consecutive.
- Exclusion criteria: reported lose or watery stools > 25% of the BM, laxative/enema abuse, ischemic colitis, surgeries (GI, Abdominal, etc.), chronic condition associated with abdominal pain, family history of colorectal cancer (familial), drugs used that caused constipation (narcotics) except those used to treat IBS.
- 800 patients were enrolled (395 in the placebo group and 405 in the linaclotide group). The dose of linaclotide was 290 micrograms daily.
- Primary Outcomes: The FDA end point was defined as a patient who met both of the following criteria in the same week for at least 6 of the 12 weeks of the treatment period: (i) an improvement of ≥30% from baseline in the average of the daily worst abdominal pain scores and (ii) an increase of ≥1 CSBM from baseline. Other primary outcomes included an improvement of ≥30% in abdominal pain, ≥3 CSBMs and an increase of ≥1 CSBM from baseline, or a combination of the previous two measures in the same week (all of the last three had to occur 9 of 12 weeks).
- Secondary Outcomes: change from baseline in abdominal pain, abdominal discomfort, abdominal bloating, stool frequency, stool consistency, severity of straining, cramping, IBS symptom severity, constipation severity, adequate relief of IBS-C symptoms, degree of relief of IBS symptoms, and treatment satisfaction.
- The study used an Intent to Treat data handling method. The study had a power of >85% and also maintained an alpha level of 0.05 to detect any statistical significance.

RESULTS

- 325 patients in the placebo group and 305 patients in the linaclotide group completed the entire study.
- Primary Outcomes: the FDA end point showed a statistical significance with a P value < 0.0001 and a NNT of 8; the other three primary measures include >30% pain reduction for 9/12 wks with a p value of 0.0263 (NNT 13.8), 3 or more CSBMs and an increase from baseline 9/12 wks p value of < 0.0001 (NNT 7.6) and finally the combination of the two end points above with a p value of 0.0004 (NNT 14.2)
- All secondary outcomes show statistical significance.
- The authors conclude that linaclotide significantly improved abdominal and bowel symptoms in this phase 3 trial.

STRENGTHS

- Randomization, placebo-controlled trial—typically gold standard
- Withdrawal randomization period
- Inclusion and exclusion allows for extrapolation to patients with IBS-C

LIMITATIONS

- Bias is a potential concern for this study because many authors had financial ties to the manufacturer.
- Study design prevented analysis of how each individual factor such as diet and exercise, affected the study results.

CONCLUSIONS

- Although the study design was gold standard and linaclotide showed significant difference between treatment groups, the clinical significance may be limited. Adverse drug events appear to be a bigger concern (diarrhea) then the actual difference in improvement in abdominal pain and constipation.
- Further studies should be conducted with longer study durations to determine the adverse events of linaclotide when used longer than 12 weeks.

Reference: Satish Rao MD, Anthony J Lembo MD, Steven J Shiff MD, Bernard J Lavins MD, Mark G Currie PhD, Xinwei D Jia PhD, ect. 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 Sep 18.

Prepared by Ryan Harkness, Doctor of Pharmacy Candidate.