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Efficacy and Tolerability of Guanylate Cyclase-C Agonists for Irritable Bowel Syndrome with Constipation and Chronic Idiopathic Constipation: A Systematic Review and Meta-Analysis

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Abstract

OBJECTIVES: Linaclotide and plecanatide are guanylate cyclase-C (GCC) agonists for the treatment of chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C). Our objective is to evaluate the efficacy and tolerability of GCC agonists based on data from multiple randomized controlled trials (RCTs).

METHODS: We searched PubMED, EMBASE, Cochrane databases, clinicaltrials.gov, major conference abstracts, Food and Drug Administration (FDA) websites, and United States Securities and Exchange Commission filings of drug sponsors to identify RCTs of CIC or IBS-C patients. We assessed efficacy based on FDA-approved composite responder endpoints, diarrhea as an adverse event, and study withdrawal owing to diarrhea for each therapy. Trial results were pooled using DerSimonian and Laird random effects model of meta-analysis and exact logistic regression when appropriate with 95% confidence intervals. Meta-regression was performed to compare outcomes between therapies adjusting for placebo event rate.

RESULTS: Eight linaclotide trials (five CIC; three IBS-C) and seven plecanatide trials (four CIC; three IBS-C) evaluating 10,369 patients met inclusion criteria. FDA publications documented that different definitions for diarrhea were used in linaclotide vs. plecanatide trials. Both drugs were efficacious in treating CIC (linaclotide 72 μg (Odds ratio (OR)=3.11, 95% CI 1.81–5.34); linaclotide 145 μg (OR=3.25, 2.15–4.91); plecanatide 3 mg (OR=1.99, 1.57–2.51)) and IBS-C

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SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

CONFLICT OF INTEREST

Guarantor of the article: Philip Schoenfeld.

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(linaclotide 290 μg (OR=2.43, 1.48–3.98); plecanatide 3 mg (OR=1.87, 1.47–2.38); plecanatide 6 mg (OR=1.92, 1.48–2.48)). Diarrhea occurred in excess of placebo in treating CIC (linaclotide 72 μg (OR=3.07, 1.97–4.77); linaclotide 145 μg (OR=3.70, 2.69–5.10); plecanatide 3 mg (OR=3.86, 1.83–8.12)) and IBS-C (linaclotide 290 μg (OR=8.02, 5.20–12.37); plecanatide 3 mg (OR=5.55, 1.62–19.00); plecanatide 6 mg (OR=4.13, 1.57–10.83)). Based on meta-regression, there were no statistically significant differences between therapies in odds ratios for efficacy, diarrhea, or diarrhea-related study withdrawals.

CONCLUSIONS: Both linaclotide and plecanatide demonstrate similar efficacy and tolerability in treating IBS-C and CIC. No differences in odds of diarrhea were seen between linaclotide and plecanatide.

INTRODUCTION

Irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) are common conditions associated with a significant detriment to quality of life (1–4). Two therapies, linaclotide and plecanatide, target guanylate cyclase-C (GCC) receptors on the lumen of the intestinal epithelium and have been investigated for the treatment of IBS-C and CIC. Linaclotide was approved as the first GCC agonist for the treatment of IBS-C (290 μg daily) and CIC (145 μg daily) by the Food and Drug Administration (FDA) in 2012. In 2017, the FDA-approved a 72 μcg dose of linaclotide for treatment of CIC. Also, in 2017, plecanatide was the second GCC agonist approved for the treatment of CIC (3 mg daily) and the supplemental new drug application was recently accepted for IBS-C (3 mg or 6 mg daily).

Activation of GCC receptors leads to an increase in cyclic guanosine-3’, 5’-monophosphate in both the intracellular and extracellular space. The increase in intracellular cyclic guanosine-3’, 5’-monophosphate activates the cystic fibrosis transmembrane conductance regulator, enhancing the intestinal secretion of chloride and bicarbonate and leading to increased gastrointestinal transit rates (5,6). Animal data indicate that increases in extracellular cyclic guanosine-3’, 5’-monophosphate modulate abdominal pain (7,8). Per prescribing information, “in an animal model of visceral pain, linaclotide reduced abdominal muscle contraction and decreased the activity of pain-sensing nerves by increasing extracellular cyclic guanosine-3’, 5’-monophosphate” (9). Also, per prescribing information, plecanatide “reduced abdominal muscle contractions” in an animal model of visceral pain (10).

Linaclotide binds to GCC receptors in a pH-independent manner in the acidic as well as neutral or basic portions of the small intestine and colon (5), and ~3–5% of active peptide is recovered in the stool. These data suggest that linaclotide may be active throughout the small intestine and colon. Binding of plecanatide to GCC receptors is pH-dependent with increased activity in the acidic portion of the proximal small intestine. It is unclear if any intact plecanatide could be recovered from stool as no excretion studies have been published. It is unclear if these differences may impact the efficacy or tolerability of these agents.

Diarrhea is a common side-effect of this drug class (11) and is attributed to excessive intestinal secretion from activation of GCC receptors. It has been hypothesized that the pH-

sensitive binding of plecanatide to GCC receptors in the proximal small intestine may reduce diarrhea (12–14) and numeric rates of plecanatide-associated diarrhea are lower than linaclotide in randomized controlled trials (RCTs). Although limited clinical trial data about plecanatide have been published, recent FDA publications document that Phase III RCTs of plecanatide for CIC used a more stringent definition for diarrhea compared with similar linaclotide trials (15,16). This could account for the numeric differences in diarrhea rates. No prior meta-analysis has collected RCT data for the GCC agonist class of drugs nor used odds ratios to assess efficacy and tolerability compared with controls. Therefore, the aim of this meta-analysis is to evaluate efficacy, frequency of diarrhea as an adverse event, and frequency of study withdrawal owing to diarrhea for linaclotide and plecanatide.

METHODS

Literature search and trial eligibility

This systematic review was conducted and reported in accordance with the PRISMA statement. We searched the literature using PubMED, EMBASE, Cochrane Central Register of Controlled Trials, and clinicaltrials.gov databases (December 28, 2016), as well as abstract books from DDW and ACG meetings (2005–2016). Study inclusion criteria were: (a) double-blind RCTs; (b) study patients defined as having IBS-C or CIC based on modified ROME II or ROME III criteria; (c) ≥2-week duration; (d) for efficacy analysis, comparison of linaclotide or plecanatide vs. placebo using the FDA-approved composite responder endpoint; (e) report frequency of diarrhea as an adverse event and frequency of withdrawal from study due to diarrhea; and (f) English language.

Our PubMED search string was as follows: (“linaclotide” OR “MD-1100” OR “MD 1100” OR “MD1100” OR “plecanatide” OR “SP-304” OR “SP 304” OR “SP304” OR “guanylate cyclase”) AND (“Constipation”[Mesh] OR “Irritable Bowel Syndrome”[Mesh] OR “irritable colon” OR “IBS”). Our EMBASE search string was: “linaclotide”/exp OR “linaclotide” OR “md 1100”/exp OR “md 1100” OR “md1100”/exp OR “md1100” OR “plecanatide”/exp OR “plecanatide” OR “sp 304”/exp OR “sp 304” OR “sp304”/exp OR “sp304” OR “guanylate cyclase”/exp OR “guanylate cyclase” AND (“constipation”/exp OR “constipation” OR “irritable bowel syndrome”/exp OR “irritable bowel syndrome” OR “irritable colon”/exp OR “irritable colon”). We searched clinicaltrials.gov using search terms “linaclotide” and “plecanatide”.

When we identified clinical trials not yet published in full manuscript form in peer-reviewed literature, we utilized data published in abstract form and searched relevant drug sponsor websites and EDGAR (published by the United States Securities and Exchange Commission) for 8-K reports from the relevant drug sponsor to assess trial eligibility and to extract relevant data. Data derived from EDGAR were extrapolated from reported percentages of relevant outcomes when raw event numbers were not available. All data were derived from public sources. Study sponsors (Ironwood Pharmaceuticals, Inc., and Synergy Pharmaceuticals, Inc.) reviewed raw event numbers, provided corrections as needed and verified the remaining data. The literature search, application of study eligibility criteria, and data extraction were performed independently by authors ES and PS. Discrepancies in trial eligibility or data extraction were resolved by consensus among authors.

Data extraction

A spreadsheet was created (Microsoft Excel, Microsoft, Redmond, WA, USA) regarding clinical trial phase, country of primary study site, corresponding level of care (primary, secondary, or tertiary), number of study sites, definition of IBS-C or CIC, inclusion and exclusion criteria, baseline patient characteristics (mean age, sex, abdominal pain/discomfort, and frequency of bowel movements), and dosing protocol (dose, frequency, route of administration, duration).

The Cochrane risk of bias tool was used to evaluate the quality of each study. Each eligible trial was evaluated for randomization protocol, methods of blinding and concealment, attrition from study and dataset completeness, and presence of selective reporting (17).

Study endpoints for meta-analysis

Our co-primary endpoints were therapeutic response based on FDA-approved composite responder endpoints and frequency of diarrhea as an adverse event. For IBS-C trials, the FDA-approved composite responder endpoint is decrease in weekly average of worst abdominal pain in past 24 h of ≥30% with concurrent increase in CSBM (complete spontaneous bowel movements) ≥1 per week for at least 50% of the weeks in a 12-week trial of therapy. (Note: For linaclotide IBS-C trials, the FDA-approved composite responder endpoint was not the original primary endpoint because the FDA had not approved a composite responder endpoint at onset of trial. Data for this endpoint were derived from *post hoc* analysis). The FDA-approved composite responder endpoint for CIC is defined as improvement in complete spontaneous bowel movements (CSBM) ≥1 per week with ≥3 CSBM per week for at least 75% of weeks in a 12-week trial of therapy. (Note: for plecanatide CIC trials, the new FDA-approved composite responder endpoint or sustained responder endpoint was used. This also requires positive response in three of the last 4 weeks of trial).

We also extracted from each study, by study arm, the number of participants with diarrhea. The definition of diarrhea as an adverse event was more stringent in trials assessing plecanatide vs. trials assessing linaclotide. For Phase III plecanatide trials in CIC, *"since an increase in the number of BMs from baseline was an expected pharmacodynamic effect of plecanatide and would be coded as diarrhea, sites were instructed to only record an AE of diarrhea if the patient reports that it was bothersome [e.g., watery/mushy stool (BSFS score of 6 or 7) with a sense of urgency, etc.] or if the event required treatment or hospitalization"* (15). For Phase III linaclotide trials in CIC and IBS-C, *"per protocol, patients were given the opportunity to report adverse events spontaneously. In addition, at each visit following the first visit, patients were questioned (in a non-leading manner) to volunteer information regarding any AEs that had occurred since the previous visit. Examples of questions included, "Have you had any unusual signs or symptoms since your last visit?" All verbatim terms were collected on patient's eCRF"* (16).

As a secondary endpoint, we assessed study withdrawal owing to diarrhea, which may be a better reflection of clinically important diarrhea compared with prevalence of diarrhea at any time during a research trial. Data were extracted on an intention-to-treat basis. Exploratory

continuous outcomes regarding abdominal and bowel symptoms were extracted when reported.

Statistical analysis

Data were pooled with respect to treatment indication, therapy, dosing schedule, and clinical trial endpoint for linaclotide as well as plecanatide. Descriptive statistics are reported using percentages and counts for binary data and mean for continuous data. Studies were pooled using a DerSimonian and Laird random-effects method with Forest plots constructed to display odds ratios (ORs) of the primary and secondary endpoints comparing active therapy to placebo. We then used meta-regression to compare the endpoints of linaclotide vs. plecanatide controlling for placebo arm prevalence. For diarrhea and withdrawal data where there were zero events, cells corresponding to zero events were replaced with a 0.5 value in the respective 2×2 table.(18) For events with zero counts, we also used an exact logistic regression model with fixed effects after expanding to patient-level data to confirm findings from random effects meta-analysis. The potential for publication bias was assessed using Harbord's test where appropriate. An I^2 statistic was calculated to assess between-study heterogeneity, and $I^2 \geq 50\%$ was defined as substantial heterogeneity. Statistical analysis was performed using STATA 14.2 (StataCorp; College Station, TX, USA).

RESULTS

The flowchart of literature search and study selection is reported in Figure 1. We identified eight trials of linaclotide (evaluating 2,824 patients on active therapy and 1,951 on placebo) (19–25) and seven trials of plecanatide (evaluating 3,617 patients on active therapy and 1,977 on placebo) (14,26–31). Lembo *et al.* (20) reported pooled results of two phase III linaclotide trials for CIC. The study characteristics of each trial, including registered phase of study, inclusion criteria, dosing protocol, and follow-up length are summarized in Supplementary Table 1 online. Two phase 2a trials (one of linaclotide and one of plecanatide) to treat CIC were not eligible for the efficacy analysis because either the trial length was too short (32) or the outcome was not assessed (26). The evaluated doses for linaclotide were 72 and 145 μg (linaclotide amount; equivalent to 75 or 150 μg peptide amount) per day for chronic constipation and 290 μg (linaclotide amount; equivalent to 300 μg peptide amount) per day for IBS-C. These differences in dosing were owing to bioequivalent reformulation between phase II and phase III studies, thus similar doses were pooled in this analysis. Plecanatide was dosed at 3 or 6 mg per day in CIC and IBS-C trials. Supplementary Table 2 summarizes the risk of bias across studies utilizing the Cochrane Collaboration tool. Low risk of bias was seen in all trials. Figures 2–4 summarize the efficacy and diarrhea-related outcomes for each eligible trial stratified by active vs. placebo arm of study, and additional outcomes are reported in the Supplement.

Efficacy endpoints and patient-reported outcomes in CIC trials

Linaclotide at 72 μg (OR=3.11, 95% confidence interval (CI) 1.81–5.34; number needed to treat (NNT) =12, 95% CI 6–29) and 145 μg (OR=3.25, 95% CI 2.15–4.91; NNT=10, 95% CI 6–19) doses, as well as plecanatide at 3 mg (OR=1.99, 95% CI 1.57–2.51; NNT=11, 95% CI 8–19) and 6 mg (OR=1.90, 95% CI 1.46–2.47; NNT=12, 95% CI 8–23) doses, were

more likely than placebo to meet the FDA responder endpoint for CIC (Figure 2). Heterogeneity in ORs in linaclotide 145 μg trials were moderate (I^2 =33.9%), and no study heterogeneity was identified in plecanatide trials at either dose (I^2 =0.0%).

Diarrhea-related outcomes in CIC trials

Linaclotide at 72 μg (OR=3.07, 95% CI 1.97–4.77; number needed to harm (NNH) =9, 95% CI 6–18) and 145 μg (OR=3.70, 95% CI 2.69–5.10; NNH=9, 95% CI 6–13) doses, and plecanatide at 3 mg (OR=3.86, 95% CI 1.83–8.12; NNH=27, 95% CI 11–89) and 6 mg (OR=3.96, 95% CI 2.08–7.52; NNH=27, 95% CI 13–72) doses, were more likely than placebo to be associated with diarrhea as an adverse event in CIC trials (Figure 3). There was no heterogeneity in ORs in linaclotide 145 μg trials or in plecanatide 6 mg trials (I^2 =0.0%); however, there was moderate heterogeneity in plecanatide 3 mg trials (I^2 =33.2%). There was no evidence of publication bias in linaclotide 145 μg trials (P =0.20). No assessment of publication bias can be made with the plecanatide trials, because there are not adequately available fully published manuscripts.

Linaclotide 72 μg (OR=21.00, 95% CI 1.23 to >100; NNH>100.0) and 145 μg (OR=7.84, 95% CI 2.67–23.00; NNH=53, 95% CI 17–213) doses, as well as plecanatide at 3 mg (OR=3.87, 95% CI 1.52–9.90; NNH=69, 95% CI 23–370) and 6 mg (OR=4.08, 95% CI 1.35–12.37; NNH=75; 95% CI 21–667) doses, were more likely than placebo to be associated with study withdrawal due to diarrhea in CIC trials (Figure 4). The numerically large odds ratio for linaclotide 72 μg is partly explained by zero-events in the placebo arm of the study. There was no heterogeneity identified among trials in these analyses (I^2 =0.0%). Th ere was no evidence of publication bias in linaclotide 145 μg trials (P=0.07). Analysis of study withdrawal using exact logistic regression similarly identified excess study withdrawal on linaclotide 72 μg (OR=13.88, 95% CI 2.22 to >100), linaclotide 145 μg (OR=12.36, 95% CI 3.89–62.96), plecanatide 3 mg (OR=4.20, 95% CI 1.68–12.58), and plecanatide 6 mg (OR=4.31, 95% CI 1.40–17.67).

Efficacy endpoints and patient-reported outcomes in IBS-C trials

Linaclotide 290 μg (OR=2.43, 95% CI 1.48–3.98; NNT=6, 95% CI 4–16) and plecanatide 3 mg (OR=1.87, 95% CI 1.47–2.38; NNT=9, 95% CI 6–16) and 6 mg (OR=1.92, 95% CI 1.48–2.48; NNT=9, 95% CI 6–17) were more likely than placebo to meet the FDA responder endpoint for IBS-C. There was substantial study heterogeneity identified in the linaclotide analysis (I^2=77.1%), but no study heterogeneity (I^2=0.0%) identified in the plecanatide analysis.

Diarrhea-related outcomes in IBS-C trials

Linaclotide 290 μg (OR=8.02, 95% CI 5.20–12.37; NNH=6, 95% CI 4–10) and plecanatide 3 mg (OR=5.55, 95% CI 1.62–19.00; NNH=27, 95% CI 8–192) and 6 mg (OR=4.13, 95% CI 1.57–10.83; NNH=35, 95% CI 12–185) were more likely than placebo to be associated with diarrhea as an adverse event in IBS-C trials (Figure 3). There was no study heterogeneity identified in the linaclotide analysis (I^2=0.0%) or 6 mg plecanatide (I^2=19.2%), but moderate heterogeneity was identified in analyses of 3 mg plecanatide (I^2=44.1%).

Linaclotide 290 μg (OR=15.39, 95% CI 4.19–56.55; NNH=32, 95% CI 9–141) and plecanatide 3 mg (OR=10.36, 95% CI 1.92–55.89; NNH>100) and 6 mg (OR=11.08, 95% CI 1.42–86.24; NNH>100) were more likely than placebo to be associated with study withdrawal due to diarrhea in IBS-C trials (Figure 4). There was no evidence of study heterogeneity in any analysis (I^2 =0.0%). One linaclotide trial and three plecanatide trials had zero events in the placebo arm of study. Analysis of study withdrawal using exact logistic regression was similar for linaclotide (OR=21.73, 95% CI 5.62 to >100), plecanatide 3 mg (OR=20.18, 95% CI 3.38 to >100), and plecanatide 6 mg (OR=14.17, 95% CI 2.28 to >100).

Meta-regression of efficacy and diarrhea-related outcomes

We used meta-regression of aggregate data to compare the endpoints of efficacy, diarrhea and study withdrawal owing to diarrhea between the two therapies in treating IBS-C or CIC. This was performed to control for differences in event rates in the placebo arms of trials. There were no statistically significant differences in any analysis (Table 1).

Additional outcomes

We identified additional exploratory outcomes evaluating objective improvements in bowel symptoms, as well as additional patient-reported outcomes and global improvement measures. Owing to heterogeneity in reporting, measures are reported descriptively only and no statistical analysis was performed (Supplementary Tables 3–7).

DISCUSSION

This is the first meta-analysis evaluating GCC agonists, linaclotide and plecanatide, for the treatment of CIC and IBS-C. Comprehensive data about the odds of achieving therapeutic response and diarrhea-associated adverse events are provided. Also, detailed data on study design and secondary efficacy endpoints are presented systematically. Based on meta-analysis, both linaclotide and plecanatide RCTs are well-designed and demonstrate efficacy for CIC and IBS-C. Odds ratios for efficacy endpoints overlap in linaclotide and plecanatide RCTs for both CIC and IBS-C. Also, no differences in efficacy were observed between linaclotide and plecanatide in meta-regression. Odds ratios for diarrhea as an adverse event also overlap in linaclotide and plecanatide RCTs for both CIC and IBS-C. We conclude that numeric differences in plecanatide-associated diarrhea and linaclotide-associated diarrhea are probably owing to differences in definitions of diarrhea used in these trials.

Plecanatide is a uroguanylin analog and its binding to GCC receptors is pH-dependent. Therefore, most activity is confined to the acidic portion of the proximal small intestine. Linaclotide binds to GCC receptors in a pH-independent manner (5) and active peptide is recovered in the stool, suggesting that linaclotide could be active throughout the small intestine and colon. It has been hypothesized that these differences in mechanism of action may produce lower rates of diarrhea with plecanatide (12–14).

Rates of diarrhea as an adverse event are numerically low in plecanatide Phase III RCTs, ranging from 3.2%–5.9% (Supplementary Table 8), whereas higher numeric rates of diarrhea, 5.9%–22.1%, are observed Phase III/Phase IIIb RCTs of linaclotide. However,

when making these comparisons, it is important to take into account rates of diarrhea in patients treated with placebo. In RCTs of plecanatide, placebo rates were low at 0.6–1.3%, whereas the placebo rates were higher in linaclotide trials at 2.3%–7.0%. In this meta-analysis, our use of ORs can account for numeric differences in placebo rates of diarrhea. As odds ratios overlap for primary efficacy endpoints, diarrhea, and study discontinuation owing to diarrhea, these data suggest no differences between linaclotide and plecanatide in efficacy nor tolerability. Also, meta-regression, which can control for differences in event rates in the placebo arm, show no significant difference between the two medications. Interestingly, we did not identify a dose-dependent effect on incidence of diarrhea or study withdrawal owing to diarrhea for either therapy at evaluated doses. Though there is little evidence to support a data-driven approach at this time, a practical approach toward managing patients experiencing diarrhea on guanylate cyclase-C agonists could include dose reduction.

Based on our review of FDA documents (15,16), the numerically lower rates of diarrhea for plecanatide-treated (and corresponding placebo-treated patients) is most likely due to the definition of diarrhea as an adverse event: *“since an increase in the number of BMs from baseline was an expected pharmacodynamics effect of plecanatide and would be coded as diarrhea, sites were instructed to only record an AE of diarrhea if the patient reports that it was bothersome [e.g., watery/mushy stool (BSFS score of 6 or 7) with a sense of urgency, etc.] or if the event required treatment or hospitalization.”* Whereas, in Phase III linaclotide trials in CIC and IBS-C, diarrhea was recorded as an adverse event utilizing the system for recording all types of adverse events: *“per protocol, patients were given the opportunity to report adverse events spontaneously. In addition, at each visit following the first visit, patients were questioned (in a non-leading manner) to volunteer information regarding any AEs that had occurred since the previous visit. Examples of questions included, “Have you had any unusual signs or symptoms since your last visit?” All verbatim terms were collected.”* Also, in plecanatide RCTs, patients had three site visits (weeks 4, 8, and 12), whereas patients in linaclotide RCTs had four site visits (weeks 2, 4, 8, and 12). The additional site visit at week 2 in linaclotide trials provides an additional opportunity to report diarrhea and may contribute to a higher reported rate of diarrhea in linaclotide-treated and placebo-treated patients in these trials.

This study has several important strengths and limitations. First, our efforts to use drug sponsor websites, FDA documents, and publicly available SEC filings to gather data is uncommon. Second, due to differences in events in the placebo-treated population, we used meta-regression to assess for differences in efficacy and tolerability. With respect to study limitations, there was statistically significant heterogeneity in analyses of linaclotide efficacy for both CIC and IBS-C indications. This may be partly explained by differences in eligibility criteria in a Phase IIIb RCT of CIC patients with moderate-severe bloating (21). Finally, the senior author is active as a consultant, advisory board member, and speaker on this topic for the pharmaceutical industry, which is a potential source for bias. This may be partly resolved because the senior author works as an advisory board member/consultant with the manufacturers of both linaclotide and plecanatide. Also, no industry funding was used to perform this study, and established meta-analysis principles were used to ensure an accurate presentation of data.

In conclusion, this study demonstrates efficacy for both GCC agonists in the treatment of CIC and IBS-C. No differences in efficacy or adverse events were identified between linaclotide and plecanatide. The systematic presentation of study design and secondary endpoint results in this review may facilitate future research about the efficacy, tolerability, and safety of this drug class.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- Linaclotide (72 μcg and 145 μcg doses) and plecanatide (3 mg) are GCC agonists FDA-approved for CIC. Linaclotide is approved for IBS-C and approval for plecanatide is pending.
- Diarrhea rates are lower for both plecanatide and placebo in RCTs compared with linaclotide RCTs. Prior publications opine that plecanatide may produce less diarrhea than linaclotide because of its mechanism of action.
- No prior meta-analysis has assessed RCT data for linaclotide and plecanatide.

WHAT IS NEW HERE

- In meta-analysis, both agents are efficacious in treating CIC and IBS-C. Odds ratios for efficacy, diarrhea rates, and study withdrawal due to diarrhea overlap, suggesting no significant differences between medications.
- In meta-regression, there is no statistically significant difference between medications for these endpoints.
- Per FDA reports, a more stringent definition of diarrhea as adverse event was used in RCTs evaluating plecanatide compared with RCTs of linaclotide. This is a likely reason for lower numeric rates of diarrhea associated with plecanatide.

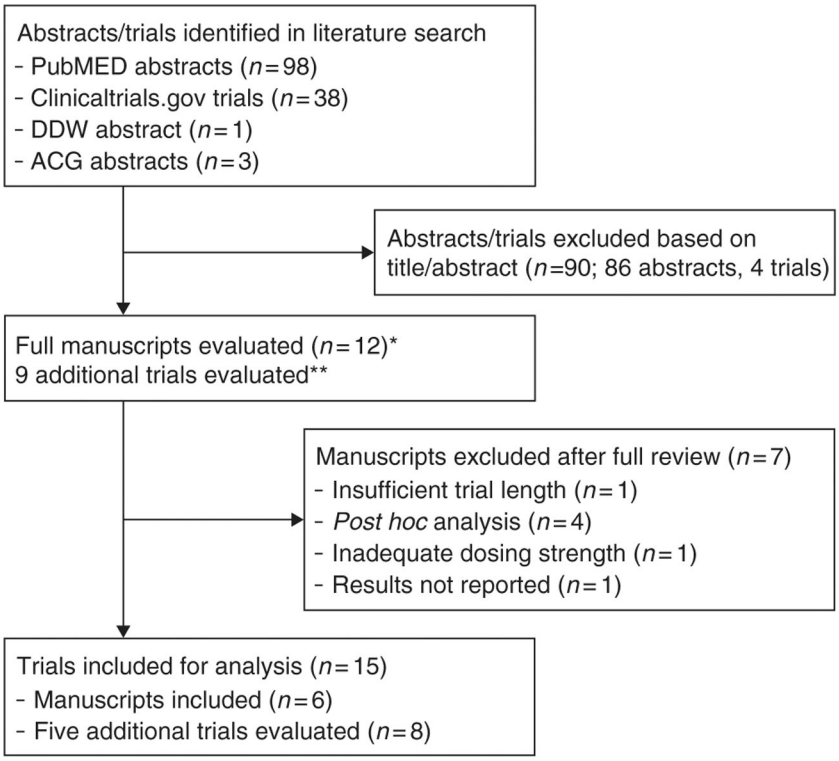

Figure 1.

Flowchart of study inclusion. *Seven trials of linaclotide were identified using clinicaltrials.gov; these trials were cross-referenced to PubMED abstracts identified in the literature search. **Four of these trials were identified in DDW and ACG proceedings. Three trials were identified in the clinicaltrials.gov search. None were published in peer-reviewed literature. Data from the abstracts were supplemented by information on clinicaltrials.gov and SEC filings to evaluate trial eligibility for this study and for data extraction.

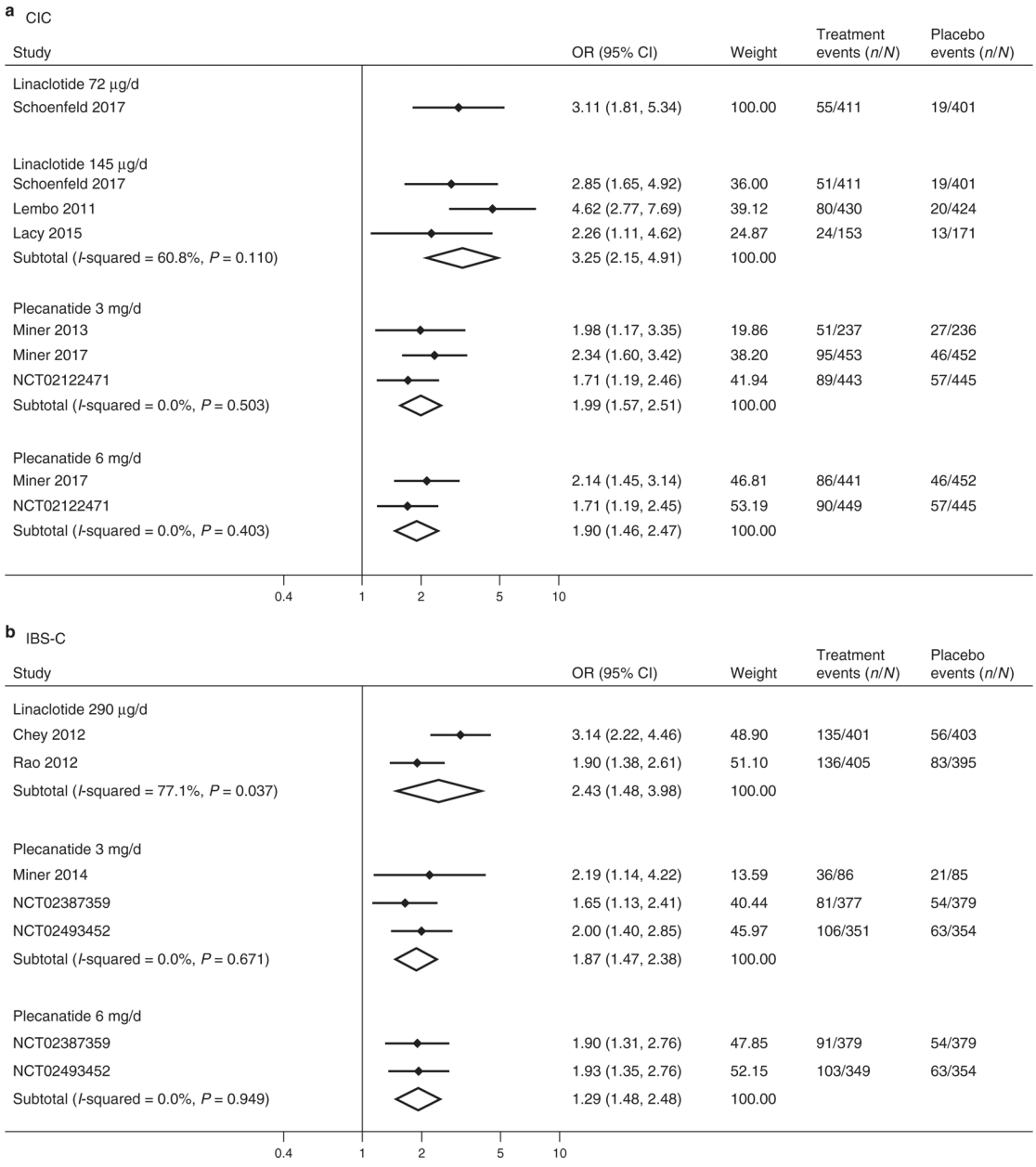

Figure 2.

Forest plots for analysis of efficacy based on FDA responder endpoint in treating CIC (**a**) and IBS-C (**b**) with linaclotide or plecanatide.

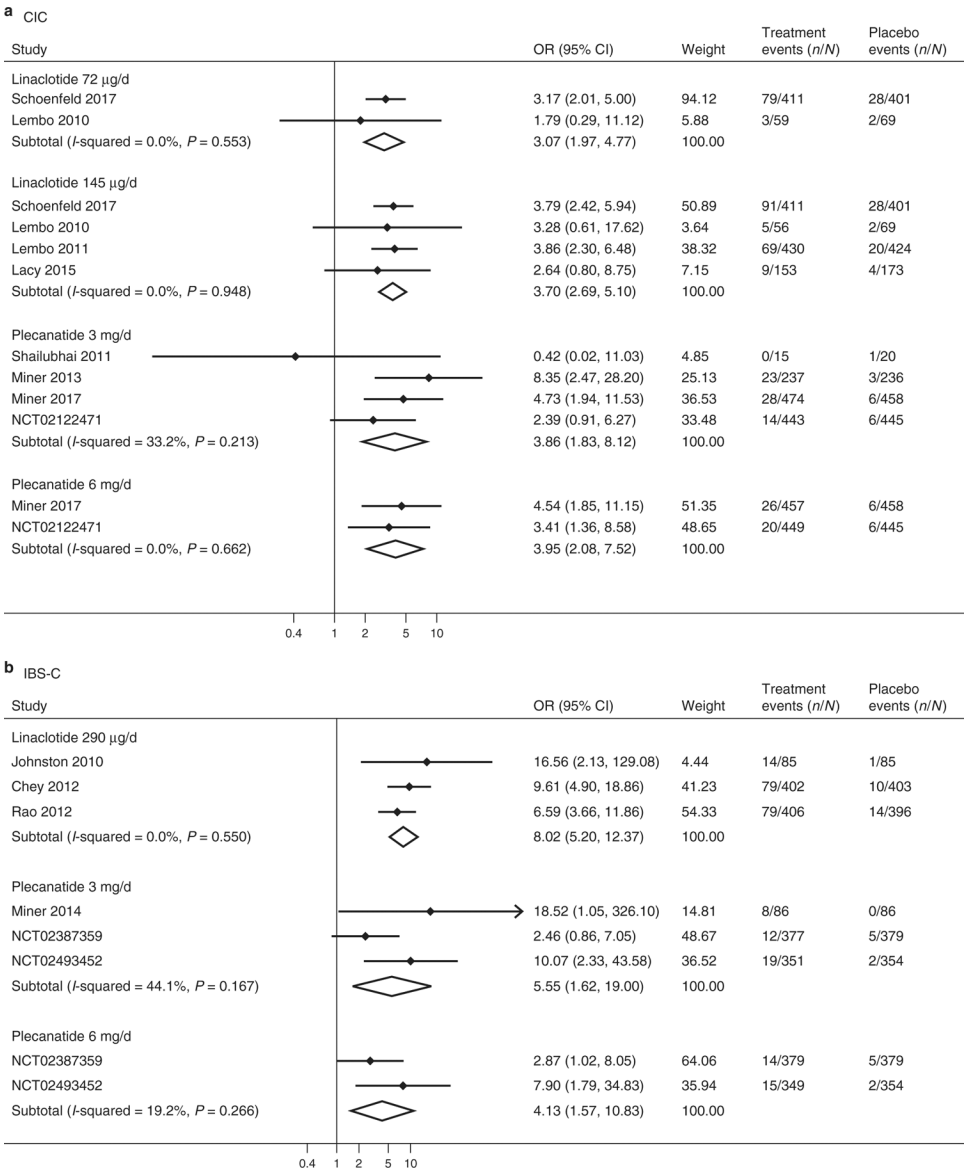

Figure 3.

Forest plots for analysis of diarrhea as an adverse event in treating CIC (**a**) and IBS-C (**b**) with linaclotide or plecanatide.

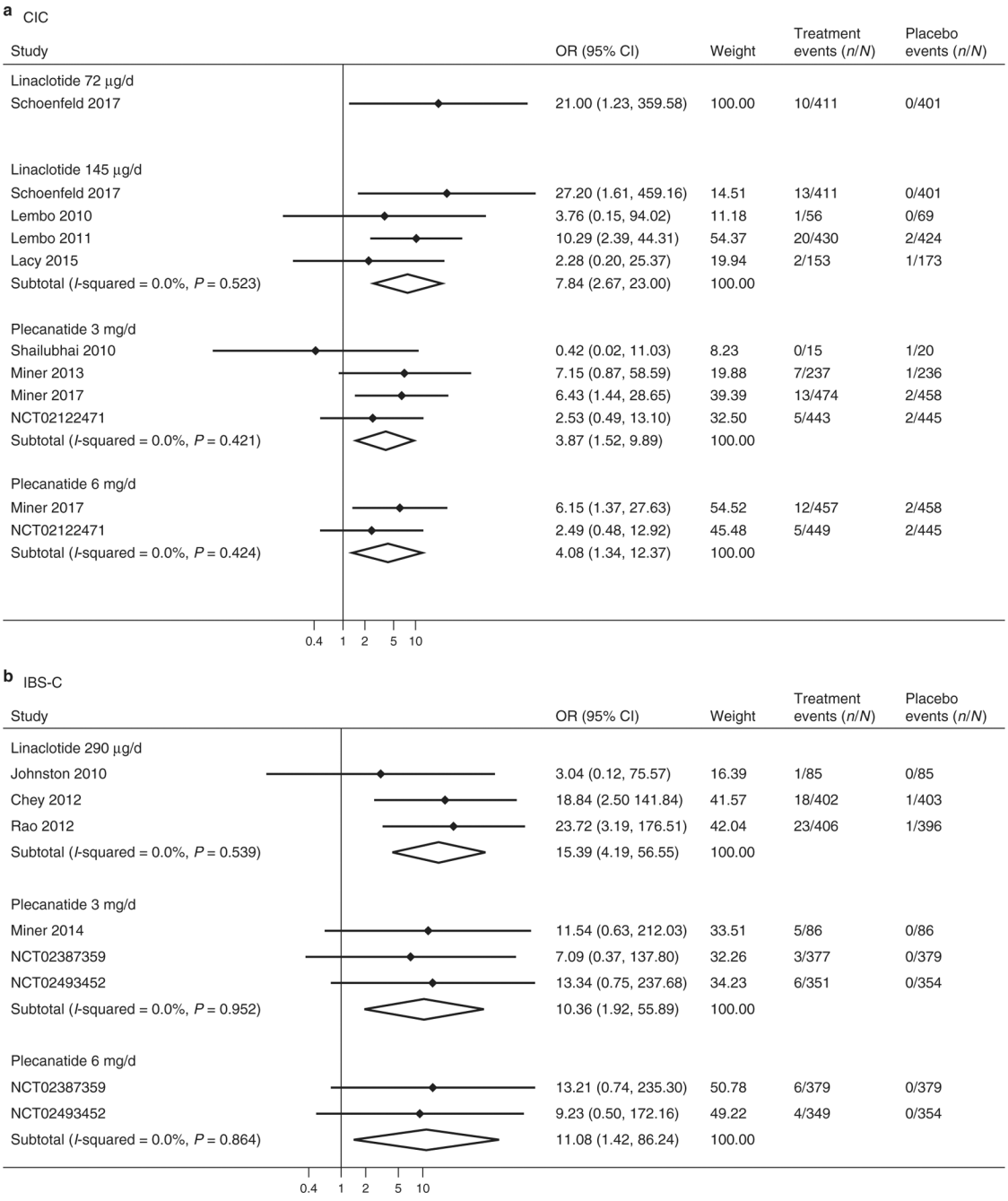

Figure 4.

Forest plots for analysis of study withdrawal due to diarrhea in treating CIC (**a**) and IBS-C (**b**) with linaclotide or plecanatide.

Table 1.

Results of meta-regression as an indirect comparison between linaclotide and plecanatide in treating CIC and IBS-C

Disease	**Chronic idiopathic constipation**		**Irritable bowel syndrome with constipation**	
Dosing	**Linaclotide 72 μg/day vs. Plecanatide 3 mg/day**	**Linaclotide 145 μg/day vs. Plecanatide 3 mg/day**	**Linaclotide 290 μg/day vs. Plecanatide 3 mg/day**	**Linaclotide 290 μg/day vs. Plecanatide 6 mg/day**
Efficacy	OR=0.77 (*P*=0.77)	OR=0.78 (*P*=0.66)	OR=1.28 (*P*=0.45)	OR=1.38 (*P*=0.34)
Diarrhea as an adverse event	OR=0.95 (*P*=0.97)	OR=0.93 (*P*=0.90)	OR=5.20 (*P*=0.13)	OR=4.72 (*P*=0.19)
Study withdrawal owing to diarrhea	OR=3.51 (*P*=0.51)	OR=1.58 (*P*=0.57)	OR=0.29 (*P*=0.55)	OR=0.27 (*P*=0.57)

There were no statistically significant differences in outcomes in any analysis.