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Efficacy and safety of olorinab, a full agonist of the cannabinoid receptor 2, for the treatment of abdominal pain in patients with irritable bowel syndrome: Results from a phase 2b randomized placebo-controlled trial (CAPTIVATE)

Lin Chang[1] | Brooks D. Cash[2] | Anthony Lembo[3] | David C. Kunkel[4] | Brett A. English[5] | Beatriz Lindstrom[5] | Guibao Gu[5] | Sharon Skare[5] | Kye Gilder[5] | Stewart Turner[5] | Fabio Cataldi[5] | Donald Lipkis[6] | Tack Jan[7]

[1]David Geffen School of Medicine, UCLA, Los Angeles, California, USA

[2]University of Texas Health Science Center Houston, Houston, Texas, USA

[3]Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

[4]University of California San Diego, La Jolla, California, USA

[5]Arena Pharmaceuticals, Inc., San Diego, California, USA

[6]Sharp Grossmont Hospital, San Diego, California, USA

[7]University Hospitals Leuven, Leuven, Belgium

Correspondence
Lin Chang, G Oppenheimer Center for Neurobiology of Stress and Resilience, 10833 Le Conte Avenue, CHS 42-210, University of California, Los Angeles 90095, CA, USA.
Email: linchang@mednet.ucla.edu

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Abstract

Background: Olorinab is a highly selective, peripherally acting, full agonist of cannabinoid receptor 2. This study assessed the efficacy and safety of olorinab to treat abdominal pain in patients with irritable bowel syndrome with diarrhea (IBS-D) and constipation (IBS-C).

Methods: CAPTIVATE was a phase 2b, randomized, double-blind, placebo-controlled, parallel-group trial. Eligible participants aged 18–70 years with IBS-C and IBS-D diagnosed per Rome IV received olorinab 10 mg, 25 mg, or 50 mg three times daily (TID) or placebo TID for 12 weeks. The primary endpoint was the change in patient-reported average abdominal pain score (AAPS) from baseline to Week 12.

Key Results: A total of 273 participants were randomized to receive olorinab 10 mg ($n = 67$), olorinab 25 mg ($n = 67$), olorinab 50 mg ($n = 69$), or placebo ($n = 70$). Although a treatment response was observed across all groups, the weekly change in average AAPS from baseline to Week 12 was not significantly different between placebo and any olorinab dose. In a prespecified subgroup analysis of participants with a baseline AAPS ≥6.5, olorinab 50 mg ($n = 35$) significantly improved AAPS compared with placebo ($n = 30$) ($p = 0.014$). Adverse event rates were comparable between olorinab and placebo and there were no reported serious adverse events or deaths.

Conclusion and Inferences: Although olorinab was well-tolerated and improved weekly AAPS, the primary endpoint was not met. However, in participants with moderate-to-severe pain at baseline (AAPS ≥6.5), olorinab 50 mg significantly improved weekly AAPS compared with placebo. ClinicalTrials.gov: NCT04043455.

KEYWORDS
abdominal pain, cannabinoid receptor agonists, cannabinoids, irritable bowel syndrome, olorinab

2 | INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic, functional disorder of the gastrointestinal (GI) tract, with an estimated worldwide prevalence of approximately 4% in the adult population, using Rome IV diagnostic criteria.[1] It is characterized by recurrent abdominal pain in association with abnormalities in stool frequency and form.[2] IBS is subtyped based on the predominant altered bowel habit, that is, diarrhea (IBS-D), constipation (IBS-C), mixed (IBS-M), or undetermined (IBS-U).[3] Functional GI disorders such as IBS have been redefined as disorders of gut–brain interaction.[4,5] Although the underlying etiology of IBS is not completely understood, evidence suggests that sensitization of visceral pain pathways induces visceral hypersensitivity, manifesting as abdominal pain.[6] Other factors implicated in IBS include mucosal immune cell activation, increased intestinal permeability, and alterations in the gut microbiota.[6–8]

Abdominal pain is often the most troublesome symptom of IBS and can significantly impair quality of life and may be debilitating.[9–11] Current pharmacological management of IBS has demonstrable symptom impact on bowel alteration, but is often less effective for controlling abdominal pain.[12,13] Antispasmodic agents are frequently prescribed off-label in the United States as first-line pain management in IBS, although most lack robust clinical data to validate their efficacy in ameliorating abdominal pain.[13,14] Other pharmacologic treatments for the abdominal pain of IBS include neuromodulators, opioid receptor modulators, GABAergic agents, probiotics, antibiotics, and secretagogues; however, side effects can be problematic with some therapies, and in many patients pain relief remains suboptimal.[2,13–15] Thus, there remains an unmet need for well-tolerated and effective pharmacologic options to manage abdominal pain in IBS.[14]

The cannabinoid receptor 2 (CB_2) is a G-protein coupled receptor subtype that is part of the endocannabinoid system and is expressed on human enteric nerves and on colonic epithelium, as well as on macrophages and plasma cells in the lamina propria.[16,17] Intestinal biopsies from patients with IBS show increased CB_2 expression,[18] and CB_2 agonists have demonstrated activity in preclinical models of visceral pain.[19,20] These findings suggest that CB_2 activation may contribute to the restoration of normal visceral sensation,[21] which may assist in ameliorating abdominal pain in IBS. Although CB_2 is predominantly expressed in the periphery and has limited central expression, the clinical development of cannabinoid receptor agonists to date has been limited by non-selectivity for CB_2 and the risk of psychoactive side effects associated with agonist activity of cannabinoid receptor type 1.[16,22]

Olorinab (APD371) is an oral, highly selective, and peripherally acting full agonist of CB_2.[22] Olorinab demonstrated more than 1000-fold selectivity for CB_2 with minimal off-target activity in a broad selectivity profiling in vitro, and low brain penetration in rats.[22] Olorinab has been shown to decrease hypersensitivity of colonic nociceptors in murine models with chronic visceral hypersensitivity, and it is proposed that olorinab-induced CB_2 activation on gastrointestinal epithelial cells, immune cells, and afferent nerves has the potential to reduce action potential firing of nociceptors and reduce pain signal transmission to the central nervous system (CNS).[23] A recent phase 2a, 8-week, open-label study of olorinab 25 mg or 100 mg three times a day (TID) in patients with active Crohn's disease showed significant improvement in abdominal pain scores and an increase in the number of pain-free days per week.[24] In an in vitro calcium imaging study using dispersed human dorsal root ganglion (DRG) sensory neurons, olorinab was found to reduce calcium influx following capsaicin activation of TRPV1 channels in both naïve and inflammatory conditions. Olorinab also reduced capsaicin responses in human DRG neurons following prolonged inflammatory soup sensitization, suggesting olorinab can be a potential novel therapy for chronic pain management, particularly in disorders characterized by visceral hypersensitivity like IBS.[25] Here, we present the results of the CAPTIVATE (APD371-202) study, evaluating the efficacy and safety of olorinab for treating abdominal pain in patients with IBS-D or IBS-C.

Keypoints

- There is a clear unmet need for effective and well-tolerated treatments to ameliorate abdominal pain in patients with irritable bowel syndrome (IBS). Olorinab, which has limited brain penetrance and a strong affinity for cannabinoid receptor 2 (CB_2) over cannabinoid receptor 1 (CB_1), may offer a novel approach to abdominal pain management in IBS and other gastrointestinal disorders.
- Here, we report the findings of CAPTIVATE (NCT04043455), a phase 2b, randomized, double-blind, placebo-controlled, multicenter trial in 273 participants with IBS.
- A treatment response was observed across all groups, and even though the primary endpoint was not met, olorinab 50 mg three times a day significantly improved average abdominal pain scores compared with placebo in a prespecified analysis of participants with moderate-to-severe abdominal pain at baseline ($p = 0.014$). Future studies to evaluate efficacy of olorinab in IBS patients with moderate-to-severe abdominal pain would be beneficial.

3 | MATERIALS AND METHODS

3.1 | Study design and treatment

CAPTIVATE was a phase 2b, randomized, double-blind, placebo-controlled, parallel-group, multicenter study conducted at 78 sites in the United States from June 2019 to January 2021. The study

comprised a screening period of up to 4 weeks, a 2-week run-in period, a 12-week treatment period, and a 2-week follow-up period (Figure 1). Eligible participants were randomized in a 1:1:1:1 ratio to olorinab 10 mg, 25 mg, 50 mg, or placebo TID for 12 weeks. The TID dosing interval was based on pharmacokinetic data from phase 1 studies in healthy participants and the phase 2a trial in Crohn's disease.[24] All participants were centrally assigned to computer-generated, randomized study treatment using an interactive web response system. Randomization was stratified by sex (male or female) and IBS subtype (IBS-D or IBS-C). To maintain blinding, the study treatments were identical in physical appearance and packaging. Treatment allocation was not disclosed to the participants, investigators, study site staff, or any other personnel involved with the clinical conduct of the study.

The CAPTIVATE study was conducted in accordance with International Conference on Harmonization Guidelines for Good Clinical Practice and principles of the Declaration of Helsinki. The protocol was approved by institutional review boards and/or independent ethics committees of all participating institutions. All participants provided written informed consent. The study was registered with ClinicalTrials.gov (NCT04043455).

3.2 | Participants

Key inclusion criteria selected for male and female participants aged 18–70 years, a body mass index 18.0–40.0 kg/m^2, and a physician diagnosis of IBS-C or IBS-D according to the Rome IV criteria.[5] Eligibility required recurrent abdominal pain ≥1 day per week, with onset of symptoms at least 6 months prior to screening. Concomitant therapy with probiotics, bulk laxatives, fiber supplements, stool softeners, and bismuth subsalicylate were allowed, provided participants had been on a stable regimen for ≥30 days prior to screening. Concomitant therapy with tricyclic antidepressants, tetracyclic antidepressants, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and nocturnally administered hypnotics (e.g., benzodiazepines or non-benzodiazepines) were also permitted for conditions other than IBS abdominal pain if participants had been on a stable regimen for ≥90 days prior to screening. Participants were required to maintain the same dose throughout the study. Rescue medication for diarrhea or constipation was not allowed during the run-in period.

Participants were required to undergo a colonoscopy prior to entering the run-in period if any of the following were present at screening: symptoms of unexplained weight loss, nocturnal symptoms, or blood mixed with stool within the previous 6 months; or a family history of colorectal cancer or inflammatory bowel disease. At the end of the run-in period participants were included if they had ≥50% of days with abdominal pain >0, an average abdominal pain score (AAPS) ≥4 (on a scale of 0–10), and diary entry compliance of ≥80%.

Key exclusion criteria included a diagnosis of IBS-M or IBS-U; clinically relevant dietary, lifestyle, or exercise changes ≤30 days prior to screening; or a history of major abdominal or colonic surgery, colorectal cancer, inflammatory bowel disease, diverticulitis, ischemic colitis, microscopic colitis, bile acid diarrhea, celiac disease, intestinal obstruction, stricture, toxic megacolon, GI perforation, fecal impaction, or impaired intestinal circulation. Excluding patients with IBS-M or IBS-U enabled this study to more clearly explore the effect or lack of effect of olorinab on predominant bowel dysfunction (i.e., stool frequency or stool consistency) after CB_2 activation, in addition to the investigation of primary and secondary endpoints with a reasonable sample size. Other GI diseases, such as peptic ulceration or functional dyspepsia, were exclusionary only if they occurred within 6 months prior to screening. Non-major abdominal procedures such as appendectomy, hysterectomy, caesarean section, or polypectomy were allowed if performed ≥3 months prior to screening. Participants taking opioids, medical or recreational marijuana, tetrahydrocannabinol, cannabidiol, synthetic cannabinoids, and cannabis derivatives within 30 days of screening were excluded, and their use was prohibited throughout the study. The use of GI-targeted antibiotics within 30 days of screening was not permitted.

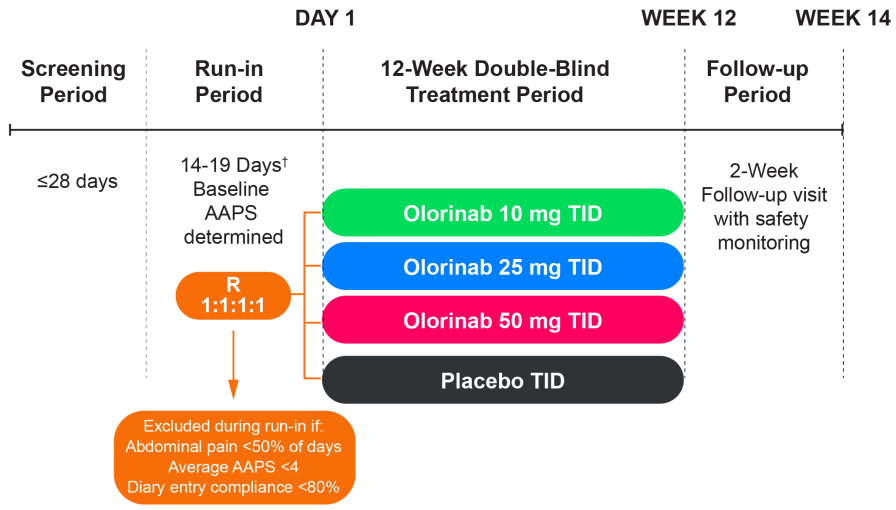

FIGURE 1 Study design of the CAPTIVATE clinical trial. AAPS, average abdominal pain scale; R, randomized; TID, three times daily. †The run-in period was up to 4 weeks for those undergoing a colonoscopy for eligibility.

3.3 | Study endpoints and assessments

The primary efficacy endpoint was the change in weekly average AAPS from baseline to Week 12. Secondary efficacy endpoints were the proportion of participants achieving ≥30% improvement in the average weekly AAPS from baseline to Week 12, and the proportion of participants achieving a sustained pain response (defined as ≥30% improvement in AAPS for ≥6 of the 12 weeks of study treatment). Key exploratory endpoints included the weekly change in AAPS from baseline to Week 12 in participants with moderate-to-severe pain at baseline, defined as those having a baseline AAPS greater than or equal to the population median (6.5 in this study). Subgroup analyses were also performed based on IBS subtype (IBS-C and IBS-D) and included the change in number of complete spontaneous bowel movements (CSBMs) per week from baseline to Week 12 in participants with IBS-C and the number of diarrhea days per week in participants with IBS-D. Diarrhea days were defined as having one or more type 6 or 7 stools using the Bristol Stool Form Scale (BSFS).[2] Current psychological symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS).[26] Separate scores were calculated for HADS anxiety (range 0–21) and depression (range 0–21), with scores of 0–7, 8–10, and 11–21 representing normal, borderline, and abnormal, respectively.

All participant-reported efficacy data were captured electronically using handheld devices. Daily electronic diary entries included an 11-point numeric rating scale to capture each participant's worst experience of abdominal pain, abdominal bloating, and abdominal discomfort during the previous 24 h. The AAPS was calculated as the average daily abdominal pain score for each weekly assessment period. Information on stool form using the BSFS, completeness of bowel movements, and confirmation of study treatment administration was also collected. Safety assessments included treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and clinically relevant changes in physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and laboratory serum chemistry, hematology, coagulation, and urinalysis assessments.

3.4 | Statistical analysis

Efficacy data were analyzed using the full analysis set (FAS), which included all randomly assigned participants, irrespective of whether they received the study drug. Safety analyses were performed using the safety set, which included all participants who received at least 1 dose of study drug. It was assumed that change in AAPS from baseline to Week 12 would be normally distributed with a standard deviation of 1.9. A sample size of 240 participants (60 per treatment group) was calculated with a two-sided 5% significance level to achieve ≥80% power to detect a treatment effect of 1.0 on AAPS between each olorinab treatment group and placebo.

Continuous endpoints, including the primary endpoint, were analyzed using a mixed-effects model repeated measures (MMRM) analysis with treatment group (placebo, olorinab 10 mg, olorinab 25 mg, olorinab 50 mg), stratification factors (sex, IBS subtype), week, and treatment-by-week interaction as factors and baseline AAPS as a covariate. MMRM models were run under the assumption of an unstructured covariance matrix. Also, alternative covariance structures were considered in the event the unstructured covariance matrix resulted in a lack of convergence.[27] Missing AAPS were not imputed for the primary analysis as MMRM utilizes all participant longitudinal data collected during the 12-week treatment period. Sensitivity analyses for the primary endpoint included analyses of covariance (ANCOVA), using observed data or multiple imputation for missing data, and Wilcoxon rank sum tests based on FAS. Categorical endpoints were analyzed using the Cochran–Mantel–Haenszel (CMH) method and logistic regression models, with sex, and IBS subtype as factors and baseline AAPS as a covariate. Time-to-event endpoints were displayed using Kaplan–Meier plots and analyzed with Cox regression models that included treatment, sex, and IBS subtype as factors and baseline AAPS as a covariate. Descriptive statistics were provided for safety assessments.

Reported p values are 2-sided and unadjusted for multiplicity. All statistical analyses were performed using SAS software (Version 9.4, SAS Institute Inc.).

4 | RESULTS

4.1 | Participants

A total of 273 participants were enrolled and included in the FAS (olorinab 10 mg TID, $n = 67$; olorinab 25 mg TID, $n = 67$; olorinab 50 mg TID, $n = 69$; placebo TID, $n = 70$), and 272 participants were included in the safety set. One participant randomized to receive olorinab 25 mg TID did not receive study treatment. Participant demographics and baseline characteristics were well balanced between treatment groups, with no notable differences in age, sex, IBS subtype, mean baseline AAPS, or in the proportion of participants with moderate-to-severe pain at baseline (baseline AAPS ≥ population median of 6.5) (Table 1). Most participants were female ($n = 197$; 72.2%), White ($n = 173$; 63.4%) had normal baseline HADS anxiety and depression scores (<8.0) ($n = 217$; 79.5% and $n = 253$; 92.7%, respectively), and completed treatment to Week 12 ($n = 230$; 84.2%). The most common reasons for study discontinuation were withdrawal ($n = 22$; 8.1%), adverse events ($n = 10$; 3.7%), loss to follow-up ($n = 4$; 1.5%), and physician decision ($n = 2$; 0.7%) (Figure 2). There were no notable differences in study completion or withdrawal due to adverse events across the four groups, although participant withdrawal was higher in the placebo group compared with olorinab treatment groups (12.9% and 6.4%, respectively).

4.2 | Efficacy

The primary endpoint of change in weekly average AAPS from baseline to Week 12 was similar between placebo and olorinab treatment

TABLE 1 Participant demographics and disease characteristics at baseline.

Demographic or characteristic	Placebo (*n* = 70)	Olorinab 10 mg (*n* = 67)	Olorinab 25 mg (*n* = 67)	Olorinab 50 mg (*n* = 69)
Age, mean/median (range), years	41.8/40.0 (20–70)	41.5/42.0 (19–67)	39.0/38.0 (18–70)	39.5/37.0 (19–70)
Female sex, *n* (%)	49 (70.0)	49 (73.1)	49 (73.1)	50 (72.5)
Race, *n* (%)				
White	50 (71.4)	38 (56.7)	46 (68.7)	39 (56.5)
Black or African American	14 (20.0)	22 (32.8)	12 (17.9)	17 (24.6)
Asian	5 (7.1)	2 (3.0)	5 (7.5)	10 (14.5)
American Indian or Alaskan Native	0	1 (1.5)	2 (3.0)	0
Not reported[a]	1 (1.4)	4 (6.0)	1 (1.5)	3 (4.3)
IBS subtype, *n* (%)				
IBS-C	35 (50.0)	33 (49.3)	34 (50.7)	34 (49.3)
IBS-D	35 (50.0)	34 (50.7)	33 (49.3)	35 (50.7)
Baseline AAPS ≥6.5, *n* (%)	30 (42.9)	36 (53.7)	36 (53.7)	35 (50.7)
Time since IBS diagnosis,[b] median (range), years	1.0 (0.1–45.3)	2.8 (0.1–39.8)	0.1 (0.1–25.6)	0.8 (0.1–30.1)
Baseline HADS for anxiety, mean (SD)	5.0 (3.54)	4.6 (3.91)	5.0 (4.16)	4.7 (4.15)
Baseline HADS for depression, mean (SD)	2.5 (2.75)	2.0 (2.51)	2.5 (2.68)	2.6 (3.00)

Abbreviations: AAPS, average abdominal pain scale; HADS, Hospital Anxiety and Depression Scale; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; SD, standard deviation.

[a]One participant who received olorinab 25 mg self-identified as multiracial and was categorized separately.

[b]Calculated relative to the date of randomization. All participants meet Rome IV criteria, including onset of symptoms ≥6 months prior to screening.

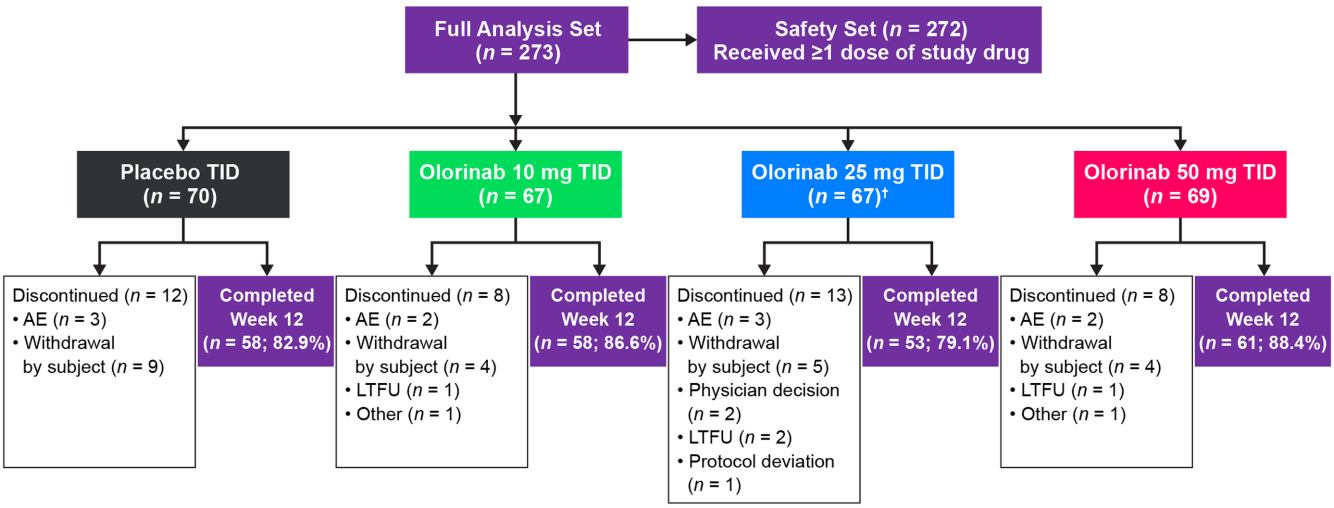

FIGURE 2 Participant disposition of the CAPTIVATE clinical trial. AE, adverse event; LTFU, lost to follow-up; TID, three times daily. †One participant in the olorinab 25-mg treatment group did not receive study drug.

groups (Figure 3A,B). Improvements in AAPS were seen in all groups, with an initial response apparent by Week 1. The least squares (LS) mean difference from placebo (*n* = 70) in the weekly average APPS from baseline to Week 12 for olorinab 50 mg (*n* = 69) was −0.55 (SE 0.401; 95% CI, −1.34 to 0.24; *p* = 0.172). AAPS from baseline to Week 12 was also similar between placebo and olorinab in pre-specified HADS-A (<8.0 [*n* = 217]; ≥8.0 [*n* = 56]) or HADS-D (<8.0 [*n* = 253]; ≥8.0 [*n* = 20]) subgroup analyses.

The proportion of participants achieving ≥30% improvement in AAPS from baseline to Week 12 was similar between the placebo (52.9%; 37/70) and olorinab treatment groups (57.6%; 117/203) (Figure 3C). The odds ratio at Week 12 with olorinab 50 mg (*n* = 69) versus placebo (*n* = 70) was 1.25 (95% CI, 0.027–2.462). Similarly, the proportion of participants who achieved a sustained pain response (≥30% improvement in AAPS for ≥6 weeks, *n* = 142/273) did not differ between treatment groups (Figure 3D). More than

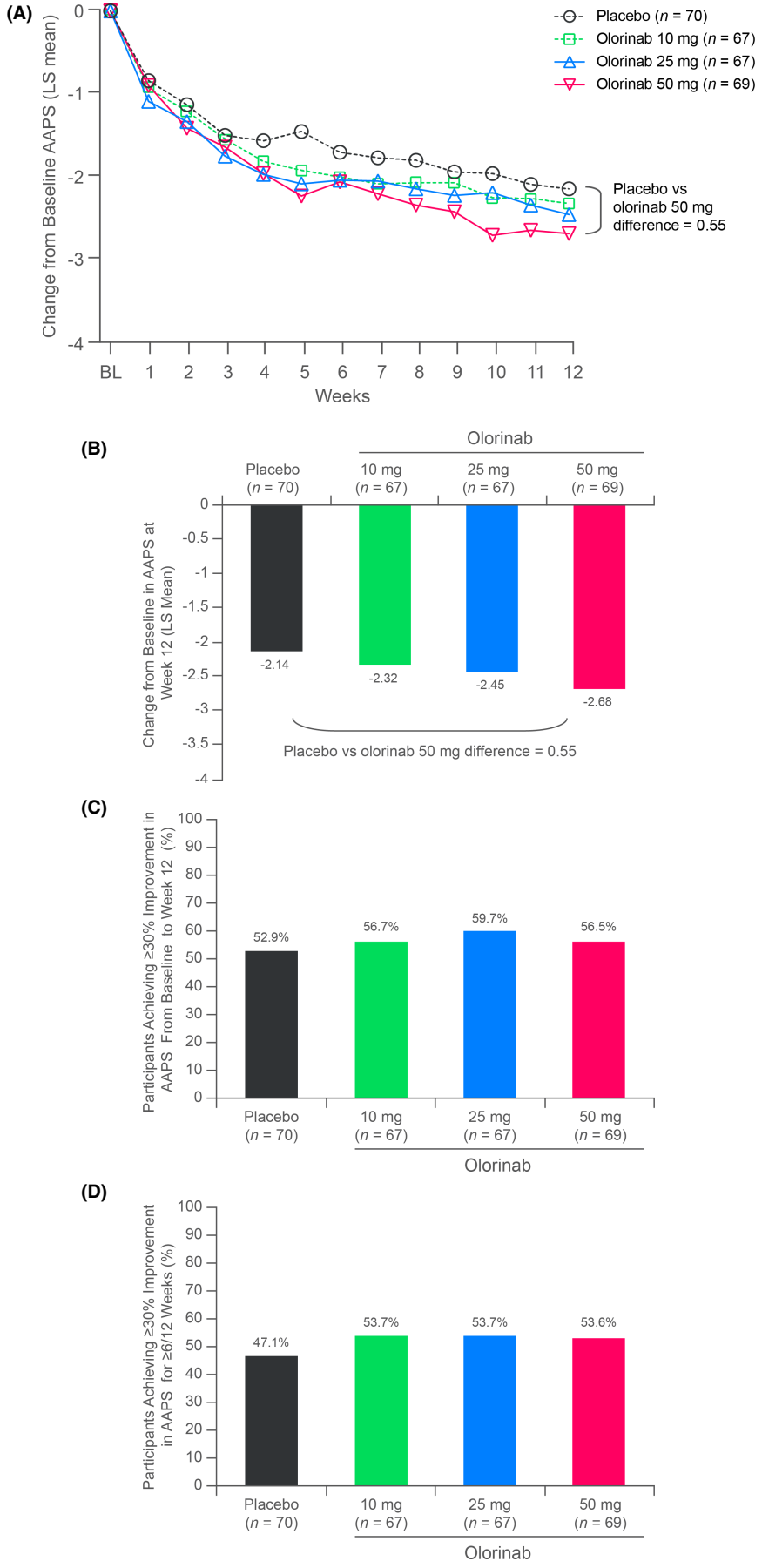

FIGURE 3 LS mean change over time in weekly AAPS score in placebo, olorinab 10-mg, olorinab 25-mg, and olorinab 50-mg groups from (A) baseline through Week 12 and (B) at Week 12. (C) Proportion of participants achieving ≥30% improvement in AAPS score from baseline to Week 12. (D) Proportion of participants achieving ≥30% improvement from baseline AAPS score for ≥6 weeks during the 12-week treatment period. AAPS, average abdominal pain scale; BL, baseline; LS, least squares.

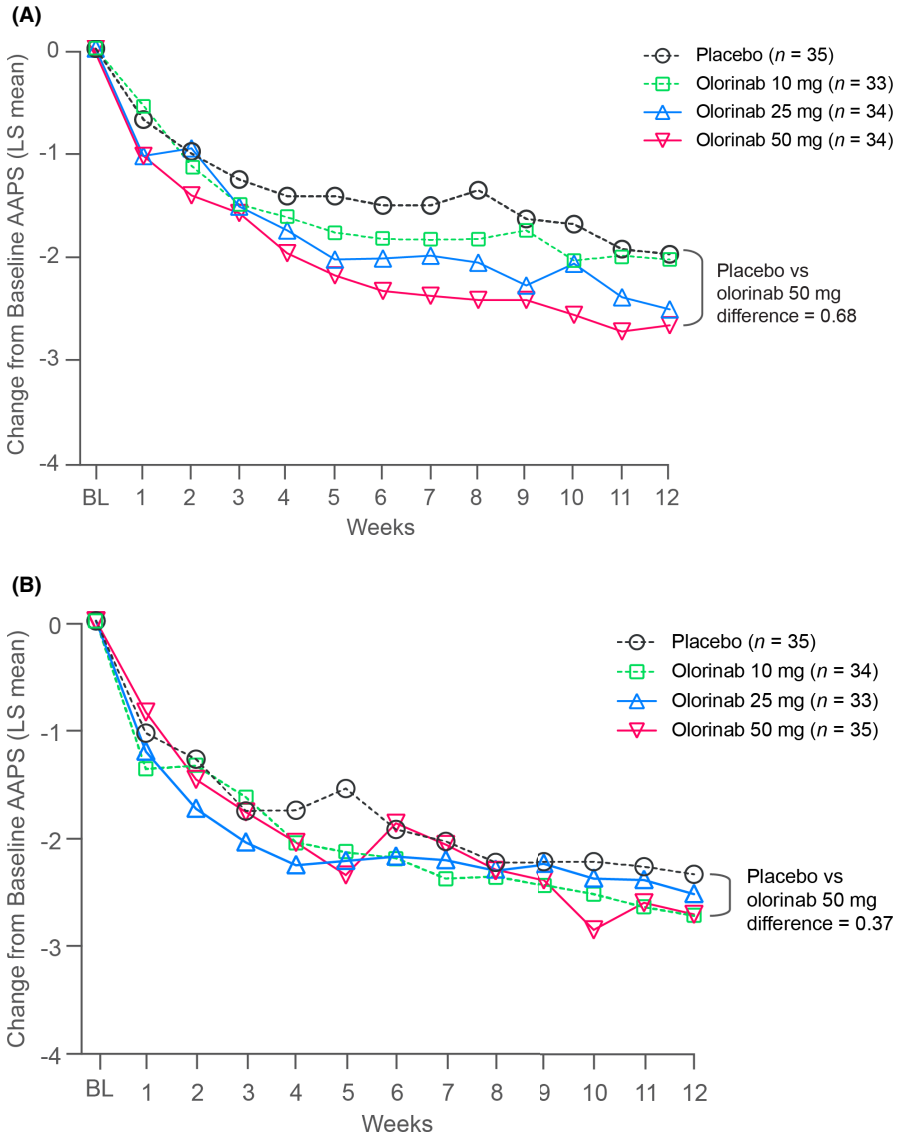

FIGURE 4 LS mean change over time in weekly AAPS score in placebo, olorinab 10-mg, olorinab 25-mg, and olorinab 50-mg groups from baseline through Week 12 in (A) participants with IBS-C and (B) participants with IBS-D. AAPS, average abdominal pain scale; BL, baseline; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; LS, least squares.

half of all participants achieved a sustained pain response (olorinab 10 mg, 53.7%; olorinab 25 mg, 53.7%; olorinab 50 mg, 53.6%; placebo, 47.1%). The odds ratio for a sustained pain response with olorinab 50 mg ($n = 69$) versus placebo ($n = 70$) was 1.23 (95% CI, 0.025–2.428).

The weekly change in AAPS between the placebo and olorinab 50-mg groups appeared to be numerically greater in participants with IBS-C ($n = 136$; Figure 4A) than in participants with IBS-D ($n = 137$; Figure 4B), although the change did not reach statistical significance in either group. The LS mean difference between olorinab 50 mg and placebo at Week 12 was −0.68 (SE 0.542; 95% CI, −1.75 to 0.39; $p = 0.211$) in participants with IBS-C ($n = 34$ vs. $n = 35$, respectively) and −0.37 (SE 0.597; 95% CI, −1.55 to 0.81; $p = 0.536$) in participants with IBS-D ($n = 35$ vs. $n = 35$, respectively).

In a prespecified analysis, the decrease in weekly AAPS at Week 12 was significantly larger in the olorinab 50-mg group ($n = 35$) compared with placebo ($n = 30$) in participants with moderate-to-severe pain at baseline (AAPS greater than or equal to the population median of ≥6.5, $n = 65$) (LS mean difference of −1.64 [SE 0.655]; 95% CI, −2.94 to −0.34; $p = 0.014$) (Figure 5A). Post hoc analysis of participants with moderate-to-severe pain according to IBS subtype showed that the effects of olorinab 50 mg compared with placebo were more pronounced in participants with IBS-C ($n = 18$ vs. $n = 16$, respectively) (Figure 5B) than in IBS-D ($n = 17$ vs. $n = 14$, respectively) (Figure 5C). A significant difference was observed in change in weekly AAPS from baseline to Week 12 for olorinab 50 mg compared with placebo in participants with IBS-C ($n = 12$ vs. $n = 13$, respectively) (LS mean difference −2.39 [SE 0.835]; 95% CI, −4.06 to −0.72; $p = 0.006$); no significant difference was observed in participants with IBS-D ($n = 12$ vs. $n = 13$, respectively) (LS mean difference −0.86 [SE 0.885]; 95% CI, −2.62 to 0.89; $p = 0.333$).

Improvement in the number of CSBMs per week in participants with IBS-C was seen in all treatment groups (Figure 6A). The LS mean difference in number of CSBMs per week between placebo ($n = 35$) and the olorinab 50-mg group ($n = 34$) at Week 12 was −0.08 (SE 0.831; 95% CI, −1.73 to 1.57; $p = 0.923$). There were no differences in the mean number of diarrhea days per week from

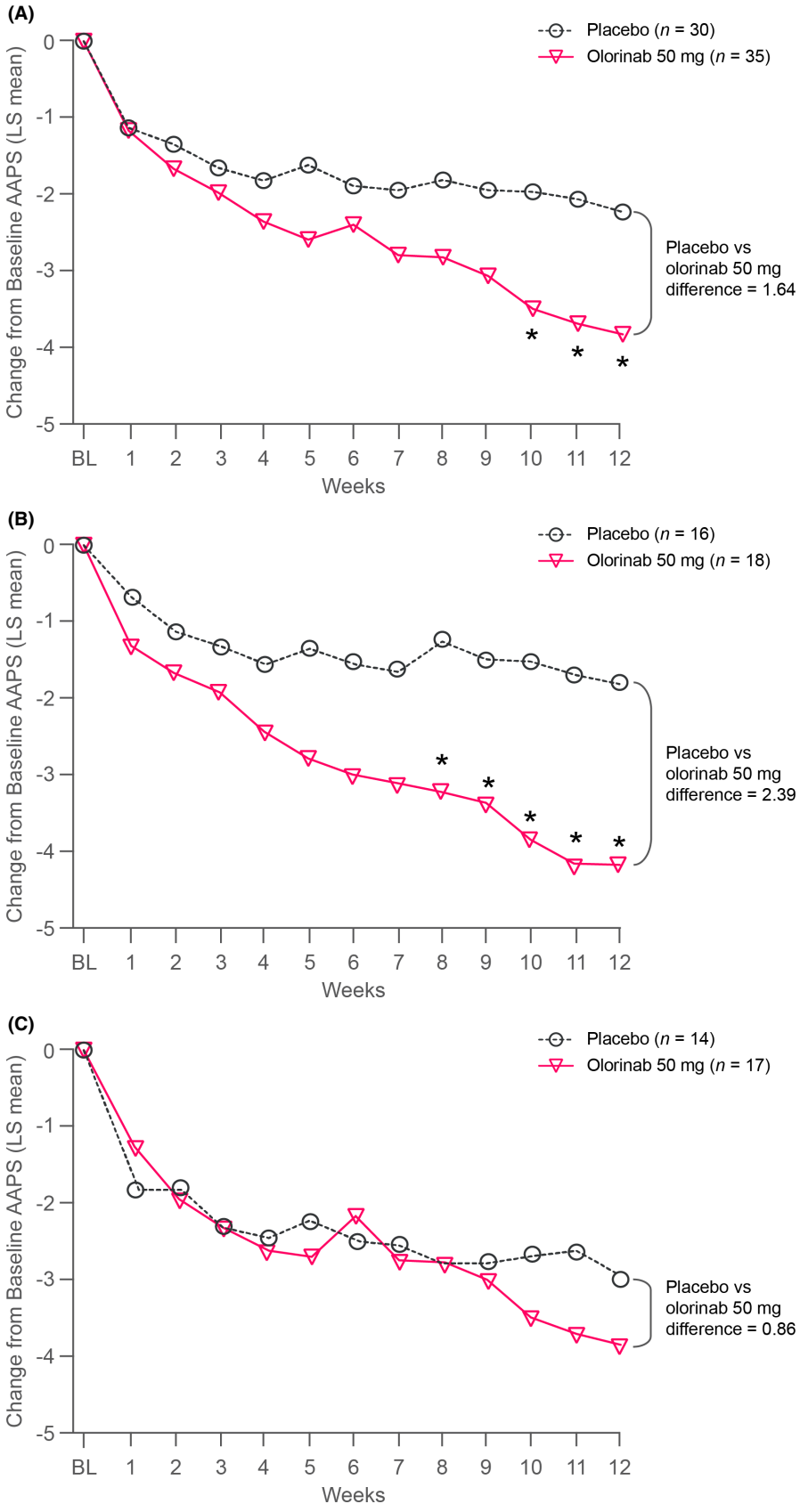

FIGURE 5 LS mean change in weekly AAPS score in placebo and olorinab 50 mg TID from baseline through Week 12 in participants with baseline AAPS ≥6.5 for (A) all participants; (B) participants with IBS-C subtype; and (C) participants with IBS-D subtype. AAPS, average abdominal pain scale; BL, baseline; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; LS, least squares.

baseline to Week 12 between the placebo group and the olorinab treatment groups in IBS-D (Figure 6B). The LS mean difference in number of diarrhea days per week between placebo ($n = 35$) and the olorinab 50-mg group ($n = 35$) at Week 12 was −0.06 (SE 0.698; 95% CI, −1.45 to 1.32; $p = 0.926$). Treatment with olorinab did not worsen bowel habits in participants with IBS-C or IBS-D.

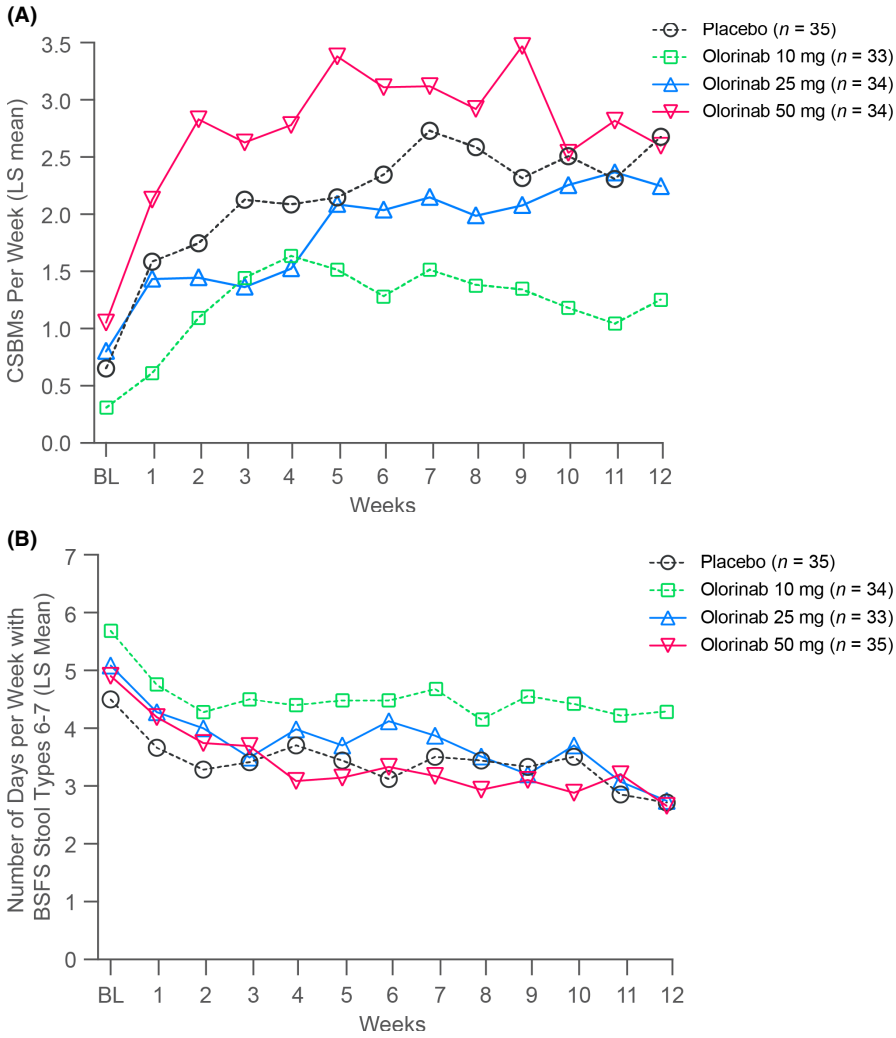

FIGURE 6 (A) LS mean change in number of CSBMs per week in placebo, olorinab 10-mg, olorinab 25-mg, and olorinab 50-mg groups from baseline through Week 12 in participants with IBS-C; (B) LS mean change in number of days per week with BSFS stool types 6–7 in placebo, olorinab 10-mg, olorinab 25-mg, and olorinab 50-mg groups from baseline through Week 12 in participants with IBS-D. AAPS, average abdominal pain scale; BL, baseline; BSFS, Bristol Stool Form Scale; CSBMs, complete spontaneous bowel movements; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; LS, least squares.

4.3 | Safety

TEAEs through to Week 12 are reported in Table 2. The proportion of participants who experienced at least one TEAE was similar across all treatment groups (olorinab 10 mg, 50.7%; olorinab 25 mg, 50.0%; olorinab 50 mg, 44.9%; placebo, 50%). Most TEAEs were mild or moderate in severity, and there were no deaths or SAEs during the study period. The most frequently reported TEAEs across all treatment groups were nausea (5.5%), headache (4.8%), nasopharyngitis (3.7%), dizziness (2.9%), dry mouth (2.6%), and upper respiratory tract infection (2.6%). Nausea was more frequently reported in participants who received olorinab (14/202, 6.9%) than in those who received placebo (1/70, 1.4%). There were no clinically meaningful changes in changes in heart rate, ECG readings, or physical examinations, although one participant in the olorinab 10-mg group discontinued treatment because of a TEAE of increased blood pressure and one participant in the olorinab 25-mg group discontinued treatment because of a TEAE of orthostatic hypotension. Both events were rated by the investigator as either mild or moderate in severity and probably related to study drug. One participant in the olorinab 50-mg group experienced a TEAE of elevated liver transaminases, and the drug was subsequently discontinued. There were no other liver-related symptoms, and the event was rated by the principal investigator as mild and probably related to study treatment.

5 | DISCUSSION

The CAPTIVATE phase 2b trial evaluated three doses of olorinab (10 mg, 25 mg, and 50 mg) administered TID for 12 weeks. Olorinab treatment at all dose levels led to a clinically meaningful reduction in AAPS scores in patients with IBS, as defined by a ≥ 2.2-point change (the minimally clinically important difference value).[28] However, there was no statistical difference between any olorinab dose versus placebo in the reduction in the average weekly AAPS from baseline to Week 12, or in the proportion of pain responders (≥30% reduction in AAPS) at Week 12, and the study did not meet its primary or secondary endpoints. In a prespecified subgroup analysis, participants with moderate-to-severe abdominal pain at baseline (AAPS ≥6.5) randomly assigned to olorinab 50 mg TID did show a statistically significant improvement in weekly AAPS at Week 12 compared with placebo. Olorinab administered TID for 12 weeks was safe and well-tolerated with no worsening of diarrhea or constipation.

TABLE 2 Summary of treatment-emergent adverse events.

Participants experiencing TEAEs, *n* (%)	Placebo (*n* = 70)	Olorinab 10 mg (*n* = 67)	Olorinab 25 mg (*n* = 66)	Olorinab 50 mg (*n* = 69)
Any TEAE[a]	35 (50.0)	34 (50.7)	33 (50.0)	31 (44.9)
TEAE related to study treatment	7 (10.0)	9 (13.4)	8 (12.1)	10 (14.5)
TEAE leading to study treatment discontinuation	3 (4.3)	3 (4.5)	4 (6.1)	2 (2.9)
TEAE occurring in >3% of participants in any treatment group				
Nausea	1 (1.4)	6 (9.0)	3 (4.5)	5 (7.2)
Headache	2 (2.9)	6 (9.0)	2 (3.0)	3 (4.3)
Nasopharyngitis	1 (1.4)	5 (7.5)	1 (1.5)	3 (4.3)
Dizziness	1 (1.4)	4 (6.0)	1 (1.5)	2 (2.9)
Dry mouth	1 (1.4)	3 (4.5)	1 (1.5)	2 (2.9)
Upper respiratory tract infection	1 (1.4)	1 (1.5)	0	5 (7.2)
Urinary tract infection	4 (5.7)	1 (1.5)	1 (1.5)	0
Abdominal pain	0	3 (4.5)	1 (1.5)	1 (1.4)
Somnolence	0	3 (4.5)	0	3 (4.3)
Gastroesophageal reflux disease	0	0	0	3 (4.3)
Bronchitis	0	0	3 (4.5)	0

Abbreviation: TEAE, treatment-emergent adverse event.

[a]There were no serious adverse events or deaths in the study.

The United States Food and Drug Administration defines a clinically significant abdominal pain "response" to therapy in patients with IBS as a ≥ 30% decrease in patient-reported weekly average worst daily pain for ≥6 weeks for a 12-week treatment period.[29] However, many patients with IBS have failed to meet this criterion for improvement in abdominal pain in pivotal randomized controlled trials of new therapeutic agents targeting IBS-C and IBS-D.[30–32] Effective, long-lasting, and well-tolerated treatment of abdominal pain is therefore an unmet need in IBS.[13,14] Olorinab may offer a well-tolerated, novel approach to abdominal pain management in IBS.

A limitation in the CAPTIVATE study was the considerable treatment response observed in participants receiving placebo. Substantial placebo response rates have been documented in other therapeutic trials for disorders of gut–brain interaction, for which objective disease measurements and biomarker endpoints are not readily available. Placebo responses with participant-reported endpoints are typically around 30%–40% in patients with IBS[33,34] and can be as high as 80% in trials having less than 12 weeks treatment duration.[35,36] Proposed reasons for high placebo response rates include patient expectation of clinical benefit, the supportive effect of being entered into a trial, cyclical variation in symptom severity, and a greater focus by both the investigator and patient on abdominal pain versus altered bowel habit.[35,37] A placebo analgesic effect mediated through the endogenous opiate system has also been proposed,[37] and studies have observed heightened activity following administration of placebo analgesia in affective and cognitive brain regions in patients with IBS compared with healthy controls.[38]

Psychological factors, such as anxiety and depression, have long been suspected in playing a role in amplifying overall pain responses and the placebo effect.[39–41] In this study, current anxiety and depression symptoms were within normal range in about 80% and 93% of study participants, respectively. Furthermore, subgroup analyses showed similar changes in AAPS from baseline to 12 weeks in those with and without normal HADS scores. This suggests that current psychological symptoms did not significantly affect subjective pain responses to olorinab or placebo in this study population.

In a previous study of women with IBS-C receiving 12 weeks of placebo therapy, a greater variability in baseline abdominal pain scores and maximum pain severity at baseline were both associated with a higher placebo response.[42] However, in the current study it appears that the placebo effect was less pronounced in participants with a higher pain severity at baseline, for whom statistically significant results were observed. Similar findings have also been reported in inflammatory bowel disease, with disease severity at baseline being an important differentiating factor in the effect of a therapeutic over placebo.[43,44]

In this trial, a greater effect of olorinab 50 mg TID over placebo was observed in participants with IBS-C, with a significant difference being observed in participants with IBS-C who had moderate-to-severe abdominal pain at baseline. This effect does not seem to be related to changes in CSBMs as these were similar between placebo and olorinab 50-mg treatment groups (Figure 6). The exact mechanism is unclear, but the placebo effect in the IBS-D participants appeared to be greater (Figures 5B,C), which might have undermined the drug effect. Characteristics of abdominal pain manifestation such as intensity, frequency, persistency, and relationship to bowel movements are

known to differ among IBS subtypes.[10] Shah et al reported abdominal pain symptoms were more frequent, widespread, and disruptive to daily activities in individuals with IBS-C compared with IBS-D.12

It is also worth noting that in the current study the assessment of pain intensity was the same for participants with IBS-C and IBS-D and involved a rating scale of the worst pain experienced over the preceding 24 h. If pain is perceived differently between IBS-C and IBS-D, this may potentially lead to differences in how abdominal pain symptoms are reported and categorized. Future studies could also consider accounting for differences in the perception of abdominal pain among IBS subtypes in the study design.

6 | CONCLUSION

Treatment with any dose of olorinab for 12 weeks was not superior to placebo in reducing weekly average abdominal pain scores in IBS. However, in a prespecified subgroup analysis, olorinab 50 mg TID did show a clinically meaningful and statistically significant improvement compared with placebo in abdominal pain scores in participants with moderate-to-severe pain at baseline (i.e., AAPS ≥6.5), with the improvement being predominately seen in participants with IBS-C. Future studies to evaluate olorinab efficacy in patients with IBS, particularly in those with moderate-to-severe abdominal pain, would be beneficial.

AUTHOR CONTRIBUTIONS

Lin Chang, Brooks D. Cash, Anthony Lembo, and Stewart Turner contributed to the study design and data analysis. Brett A. English, Beatriz Lindstrom, and Kye Gilder contributed to the study design, data collection, and data analysis. Guibao Gu and Fabio Cataldi contributed to data collection and data analysis. Sharon Skare and David C. Kunkel contributed to the study design and data collection. Donald Lipkis contributed to the data collection. All authors revised the manuscript critically for important intellectual content and reviewed the final draft.

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CONFLICT OF INTEREST STATEMENT

LC has served as an advisor for Arena Pharmaceuticals and Ironwood Pharmaceuticals; has received research grant funding from AnX Robotica, Arena Pharmaceuticals, and Ironwood Pharmaceuticals; has served as a consultant for Arena Pharmaceuticals, Immunic, Ironwood Pharmaceuticals, Mauna Kea Technologies, and Trellus; has served as a speaker for AbbVie; and holds stock options for ModifyHealth and Trellus. BDC has served as a consultant for Arena Pharmaceuticals, AbbVie, Salix Pharmaceuticals, QOL Medical, and Ironwood Pharmaceuticals; and has participated in speaker bureaus for AbbVie, Salix Pharmaceuticals, and QO Medical. AL has served as a consultant and advisor for Arena Pharmaceuticals, Allakos, Ironwood Pharmaceuticals, Takeda, Bayer, Mylan (Viatris), Shire (Takeda), Bellatrix Pharmaceuticals, Mauna Kea Technologies, Neurogastrx, Vibrant, and OrphoMed. DCK is a consultant for Salix Pharmaceuticals, GI Supply, Laborie, Redhill Biopharma, Takeda, Alfasigma, Pfizer, Ardelyx, Phathom, and Evoke Pharma. BAE, BL, GG, SS, KG, ST, and FC are current or former employees of and have or had ownership interest in Arena Pharmaceuticals. DL has nothing to disclose. JT has served as an advisor for Adare Pharmaceuticals, Alfa Wassermann Pharma, Allergan (AbbVie), Arena Pharmaceuticals, Bayer, Chr. Hansen, Clasado Biosciences, Danone, Devintec Pharma, Dr Falk Pharma, Grünenthal, Ironwood Pharmaceuticals, Janssen, Kyowa Kirin, Menarini Group, Mylan (Viatris), Neurogastrx, NeuTec Pharma Ltd, Novartis, Noventure, Nutricia, Shionogi, Shire (Takeda), Takeda, Theravance Biopharma, Tramedico, Truvion Healthcare, Shanghai Tsumura Pharmaceuticals Co, Zealand Pharma, and Zeria Pharmaceutical Co; has received research support from Shire (Takeda), Sofar S.p.A, Takeda, and Shanghai Tsumura Pharmaceuticals Co; and has participated in speakers' bureaus for Abbott, Allergan (AbbVie), AstraZeneca, Janssen, Kyowa Kirin, Menarini Group, Mylan (Viatris), Novartis, Shire (Takeda), Takeda, Truvion Healthcare, and Zeria Pharmaceutical Co.

ORCID

Lin Chang https://orcid.org/0000-0001-6800-2967

Anthony Lembo https://orcid.org/0000-0002-4479-1188

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