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Effects of treatment with eluxadoline on abdominal pain in patients with IBS-D: Additional post hoc analyses of Phase 3 trials

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Abstract

Background: Recurring abdominal pain is a characteristic and often unpredictable and debilitating symptom of irritable bowel syndrome with diarrhea (IBS-D). Measuring the effects of IBS-D treatments on abdominal pain remains a significant challenge in clinical trials. Here, we aimed to examine the effect of eluxadoline through various post hoc analyses.

Methods: Data from two eluxadoline Phase 3 trials were pooled over 26 weeks, comparing eluxadoline 100 mg twice daily to placebo. Worst abdominal pain (WAP) was measured daily on a 0-10 scale. WAP responder criteria were prospectively defined as a ≥30% improvement in daily WAP score on ≥50% of days. Pairwise, two-sided Cochran-Mantel-Haenszel tests assessed treatment effects. Cumulative distribution functions were used to plot WAP response rates using variations on the response criteria.

Key results: Of 1615 patients with IBS-D (66% female, mean age 46 years), 806 received eluxadoline and 809 received placebo; 48.3% and 44.0% were WAP responders (≥30% improvement), respectively (*P* value not significant). When the response threshold was increased to 50% daily WAP improvement from baseline, a significantly greater percentage of eluxadoline-treated patients versus placebo-treated patients were WAP responders (38.7% vs 32.5%, respectively; *P* = .009). At Week 26, average WAP changes from baseline were −3.4 and −3.0 points, respectively (*P* = .002).

Conclusions and Inferences: Despite small effect sizes, eluxadoline demonstrated consistent and sustained improvement in WAP compared to placebo across a range of prospective and post hoc analyses. Assessing WAP response across a range of measures is important for fully understanding a treatment's efficacy.

KEYWORDS

abdominal pain, diarrhea, eluxadoline, irritable bowel syndrome

Abbreviations: IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; WAP, worst abdominal pain.

1 | INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterized by recurrent abdominal pain with altered bowel habits. IBS affects an estimated 11% of the global population,[1] with the diarrhea-predominant subtype (IBS-D) accounting for approximately one-third of cases.[2,3] Symptoms of IBS-D include diarrhea, abdominal pain, urgency, and bloating; these can vary greatly in severity and can have a considerable impact on patients' quality of life.[4-8]

Abdominal pain is a cardinal symptom of IBS and is a key element of the Rome IBS diagnostic criteria.[2,3] Abdominal pain experienced by patients with IBS is often unpredictable and debilitating and is one of the primary reasons patients with IBS-D seek medical advice.[9] It is also a key determinant of health-related quality of life[10] and patient-reported symptom severity.[11] Currently, clinical trial measures of abdominal pain often assess worst daily pain using 11-point numerical rating scales; however, it has been suggested that other pain dimensions such as intensity, duration, frequency, and predictability should be considered.[12]

Adequate treatment of abdominal pain remains a significant challenge in IBS. Moreover, assessing the effect of new treatments on abdominal pain in clinical trials is difficult for a variety of reasons, including the subjective nature of patient-reported outcomes and high placebo response rates.[13,14]

Eluxadoline is a mixed μ- and κ-opioid receptor agonist and δ-opioid receptor antagonist that acts locally in the gastrointestinal tract and has been shown to reduce visceral hypersensitivity and regulate intestinal motility.[15] It is approved by the US Food and Drug Administration (FDA) for IBS-D in adults.[16] In two Phase 3 clinical trials, eluxadoline 100 mg taken twice daily met the primary endpoint of simultaneous improvement in stool consistency and reduction in worst abdominal pain (WAP).[17] Eluxadoline also demonstrated a consistent numerical improvement compared to placebo for the prespecified secondary endpoint of ≥30% reduction in WAP on ≥50% of days, although these results were not statistically significant.

The aim of this study was to examine the effect of eluxadoline on abdominal pain in patients with IBS-D, through analyses of the larger, pooled Phase 3 data set. This included exploring several alternative WAP endpoint definitions and examining the effect of baseline severity and variability as predictors of WAP response to treatment.

Key Points

- Abdominal pain can be challenging to measure. In Phase 3 trials for irritable bowel syndrome with diarrhea, eluxadoline did not significantly improve abdominal pain compared to placebo.
- Various statistical analyses showed a consistent, sustained improvement in abdominal pain with eluxadoline treatment. This effect is greater with stricter criteria for defining WAP response to treatment.
- As abdominal pain can be unpredictable, pain should be assessed across a range of measures to gain full understanding of a treatment's efficacy.

2 | MATERIALS AND METHODS

2.1 | Trial designs

Two randomized, double-blind, placebo-controlled, parallel-group trials (IBS-3001, NCT01553591; IBS-3002, NCT01553747) were conducted in order to evaluate the composite (pain and stool consistency) response to eluxadoline twice daily, relative to placebo, in adults with IBS-D. The results of these trials have been reported previously.[17,18] Patients were assessed according to the Rome III diagnostic criteria[19] and were eligible for inclusion if, during the week before randomization: their average score for WAP was >3.0 on a 0-10 numerical rating scale; their average stool consistency was ≥5.5, with a score of ≥5 on ≥5 days, according to the Bristol Stool Scale; and their average IBS-D global symptom score was ≥2.0 on a scale of 0-4. The total screening (pre-randomization) period was 2 weeks, with a third week allowed if not all inclusion criteria were met in the second week. Patients were excluded if they had any history of inflammatory bowel disease, celiac disease, abnormal thyroid function, pancreatitis, sphincter of Oddi dysfunction, postcholecystectomy biliary pain, alcohol abuse, or binge drinking. Patients were also excluded due to cholecystitis in the past 6 months, intestinal obstruction, gastrointestinal infection or diverticulitis in the past 3 months, known opioid allergy, pregnancy or breastfeeding, or receipt of antidiarrheal, antispasmodic, or narcotic drugs.[17]

Following the screening period, eluxadoline 75 mg or 100 mg or placebo was given orally twice daily for 52 weeks in IBS-3001 and 26 weeks in IBS-3002 (weeks 27-52 in IBS-3001 were for safety assessment only and therefore were not included in this analysis). In IBS-3002, the 26 weeks of treatment were followed by a 4-week, single-blind placebo washout period.

2.2 | Data collection and analysis

Patients recorded WAP scores daily via an electronic diary over the 182-day study duration. Characterization of responders (for all endpoints) to study drug required ≥110 days with a diary entry; those not meeting the diary compliance requirement were considered to be non-responders to study drug, regardless of improvement in symptoms. In order to reduce accidental coaching bias, investigators and their staff were not allowed to access diary records while the study was ongoing.

Data from weeks 1-26 of IBS-3001 and IBS-3002 were pooled for the statistical analyses. The placebo washout data (Month 7)

were not pooled as this information was collected in the IBS-3002 trial only. Although data for all treatment arms (eluxadoline 100 mg, eluxadoline 75 mg, and placebo) were analyzed for the Phase 3 trials, only the eluxadoline 100 mg and placebo data are presented in this post hoc analysis. This is because 100 mg is the recommended dose for most patients, whereas the 75 mg dose is recommended only for patients with hepatic impairment or those receiving concomitant OATP1B1 inhibitors.[16]

WAP responder criteria were prospectively defined as ≥30% improvement in daily WAP compared to the average baseline value, using the 50% of time rule (ie, daily WAP improvement criterion met for ≥50% of days with a diary entry). Baseline WAP was calculated as an average based on days −7 to −1 of the screening period (1 week prior to randomization). Prospective, alternative WAP responder rates at higher WAP improvement thresholds of 40% and 50% based on the 50% of time rule were also evaluated. Analysis of WAP responder rates by baseline pain severity was performed on three stratified subgroups with average WAP baseline severity scores of <5, 5–<8, and ≥8, to assess whether those with either milder or more severe pain were more likely to respond to eluxadoline treatment. Additionally, prospective variations in WAP responder criteria were analyzed as cumulative distribution functions: The first was a plot assessing how WAP responder rates changed when the percent improvement requirement was varied and the ≥50% of days requirement was kept constant; the second plot assessed how WAP responder rates changed when the percent of days aspect was varied and the ≥30% improvement in pain criterion was kept constant. These analyses allowed us to observe how the proportion of WAP responders varied as the criteria changed.

Due to the unpredictable nature of IBS-D symptoms, calculating baseline values based on a longer time period could lead to a more accurate reflection of patients' true pain severity. Therefore, post hoc analyses of WAP responder rates using different time periods during the screening phase to calculate baseline WAP were performed. The baseline average WAP score was calculated based on days −14 to −1, days −21 to −1 (whole screening period), days −14 to −8, and days −21 to −15.

Pairwise, two-sided Cochran-Mantel-Haenszel tests were used to assess treatment effects for eluxadoline 100 mg vs placebo, except for the analysis of different WAP baseline scores, for which Fisher's exact test (two-tail) was used. Analysis of covariance was used to assess WAP change from baseline for the daily scores (prospectively defined).

To ensure that no additional variance was introduced through pooling the data from two clinical trials, an analysis using a mixed effect model with study identity as a random effect and baseline WAP as a covariate was conducted, and the corresponding intraclass correlation coefficient was calculated.

3 | RESULTS

3.1 | Demographics

Of 1615 patients in the pooled data set, 806 were in the eluxadoline 100 mg group and 809 were in the placebo group. Although 809 patients were in the original eluxadoline 100 mg intention-to-treat group, two patients (one from each trial) tried to participate at more than one study site, and one patient received a dose of eluxadoline but did not undergo randomization; therefore, these three patients were not included in this analysis.[17] Patient demographics were well matched between groups, including sex (66.7% and 65.1% female, respectively) and mean age (45.0 and 46.4 years, respectively). Almost two-thirds of patients in each group reported an average WAP score at baseline of between 5 and 8 (Table 1). Diary completion was comparable across treatment arms.

3.2 | Daily WAP scores

Daily WAP scores showed a relatively rapid improvement over the first 2 months of treatment for both eluxadoline and placebo treatment groups. After this time period, the scores plateaued and were

TABLE 1 Patient demographics and baseline characteristics

	Eluxadoline 100 mg (n = 806)	Placebo (n = 809)	*P* value
Female, n (%)	538 (66.7)	527 (65.1)	.529
Mean age, years (SD)	45.0 (13.6)	46.4 (14.0)	.043
<65 years, n (%)	732 (90.8)	707 (87.4)	.031
Mean BMI, kg/m^2 (SD)	30.8 (7.8)	30.2 (7.1)	.115
Prior loperamide use, n (%)	296 (36.7)	282 (34.9)	.467
Prior cholecystectomy, n (%)	171 (21.2)	158 (19.5)	.422
Baseline WAP score, n (%)			.679
<5	185 (23.0)	180 (22.2)	
5–<8	523 (64.9)	519 (64.2)	
≥8	98 (12.2)	110 (13.6)	

Note: P values were calculated using Fisher's exact test (two-tailed).
Abbreviations: BMI, body mass index; SD, standard deviation; WAP, worst abdominal pain.

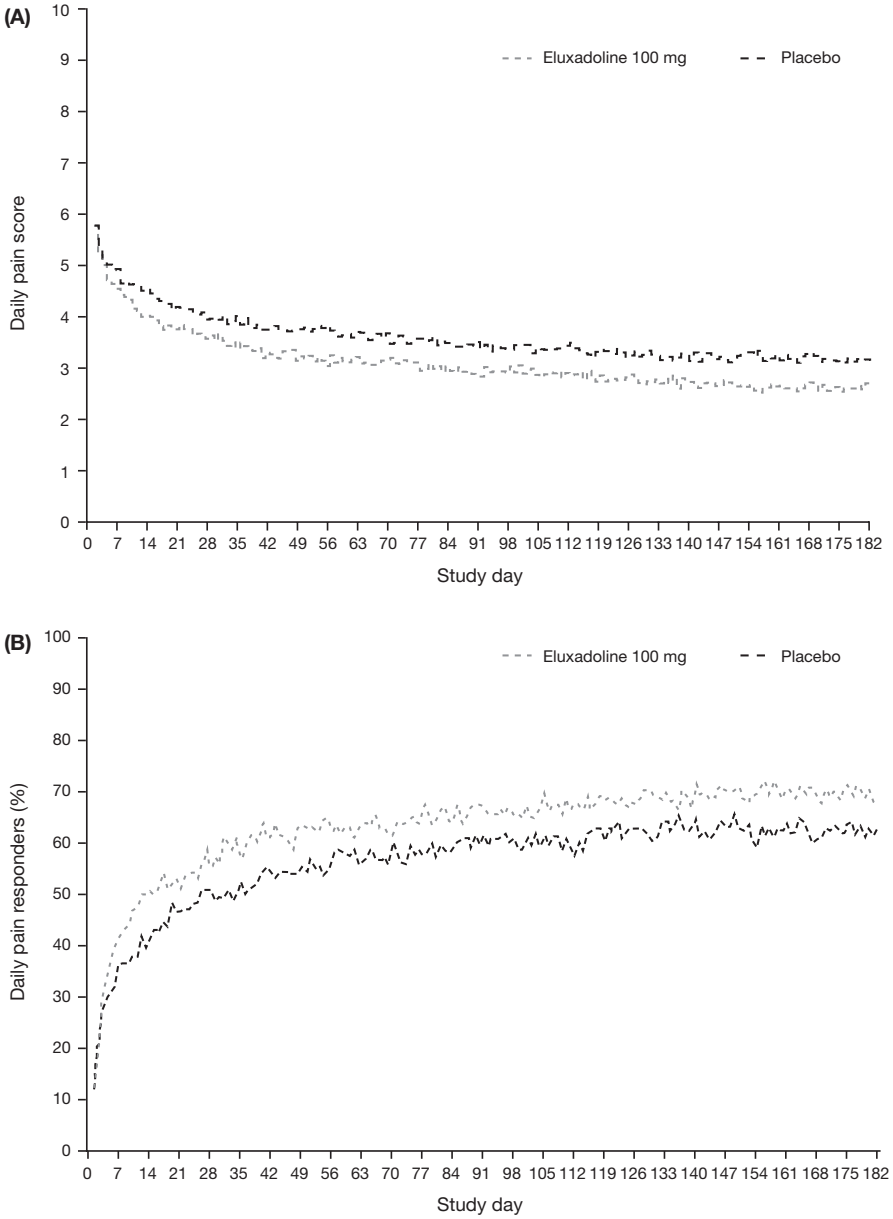

FIGURE 1 A, Daily raw abdominal pain scores. B, Percentage of patients meeting 30% WAP response criteria daily (pooled data). WAP, worst abdominal pain

sustained over the remainder of the study period (Figure 1A). While daily WAP scores decreased in both groups, separation of the curves in favor of eluxadoline was evident after approximately 1 week of treatment. At Week 26, the average change from baseline was −3.4 for eluxadoline and −3.0 for placebo (P = .002).

The percentage of patients meeting the daily WAP response criterion (≥30% improvement from baseline) also increased rapidly after the start of treatment before plateauing after approximately 1 month for both eluxadoline and placebo treatment groups (Figure 1B). Notably, a high percentage of patients on placebo regularly achieved ≥30% WAP improvement on a day-by-day basis, with over 50% of placebo patients achieving it on any given day after the first 6 weeks. Despite this, a non-significant but consistently higher WAP response rate was observed for eluxadoline compared to placebo when applying the 50% of time rule over the 26-week period for the 30% WAP response threshold (48.3% vs 44.0%, respectively; P = .086).

The analysis across studies using the mixed model yielded an intraclass correlation coefficient of 0, implying that no observed variance was introduced by pooling the two Phase 3 trials. Using this method, the interpretation of the results from the mixed model is consistent with that of the original analysis.

3.3 | WAP responder analysis: Effect of varying the percentage of pain improvement from baseline while keeping the ≥50% of days requirement constant

A cumulative distribution function analysis showed that more patients treated with eluxadoline were WAP responders compared to those on placebo for all WAP percentage improvement thresholds when applying the 50% of time rule (Figure 2). The overall magnitude of effect was greater and statistically significant when higher

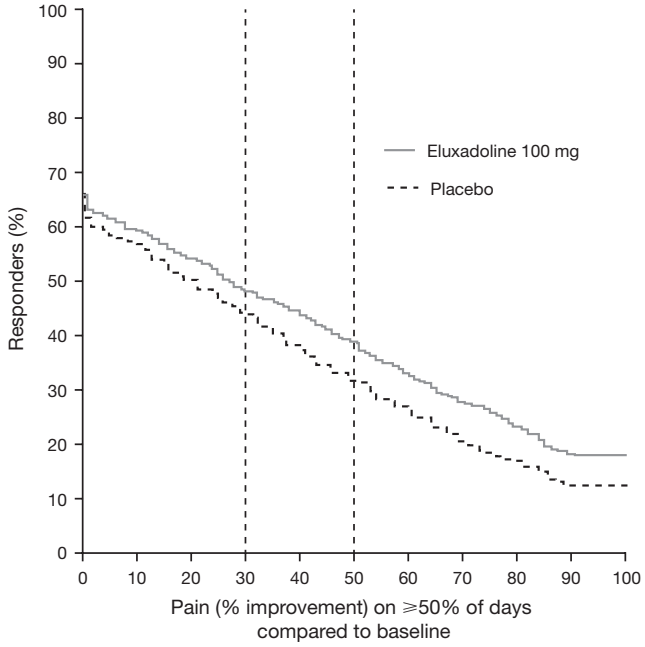

FIGURE 2 Pooled data, cumulative distribution function: percentage of patients who were WAP responders based on achieving various levels of pain improvement compared to baseline over weeks 1-26, while keeping the ≥50% of days criterion constant. WAP, worst abdominal pain

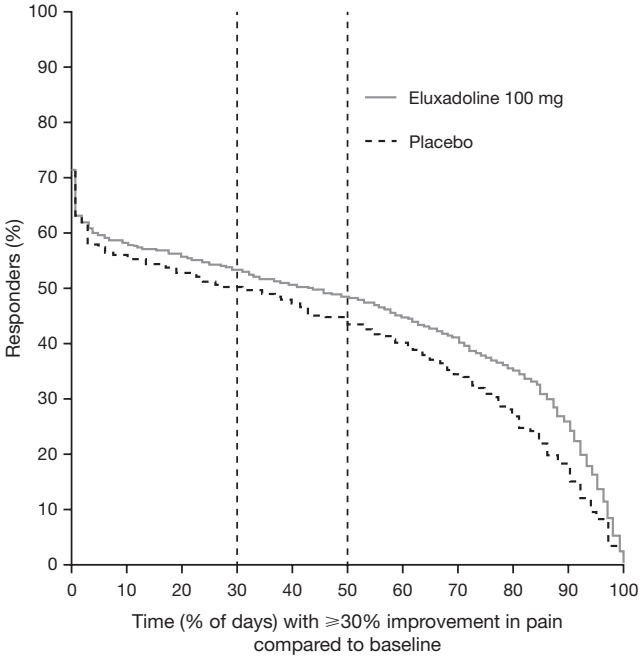

FIGURE 3 Pooled data, cumulative distribution function: percentage of patients achieving ≥30% improvement in WAP compared to baseline, varying the percentage of days required to be considered a WAP responder, over weeks 1-26. WAP, worst abdominal pain

threshold levels were examined. For example, at a threshold of 40% improvement in WAP compared to baseline on ≥50% of days, 44.2% of eluxadoline-treated patients and 37.7% of placebo-treated patients (P = .008) qualified as WAP responders, while for a 50% threshold, 38.7% of eluxadoline-treated patients and 32.5% of placebo-treated patients (P = .009) qualified as WAP responders.

3.4 | WAP responder analysis: Effect of varying the percentage of days with improvement while keeping the ≥30% pain improvement from baseline requirement constant

A cumulative distribution function (Figure 3) assessed the percentage of patients achieving ≥30% reduction in WAP for different percentages of WAP responder days. A greater percentage of patients treated with eluxadoline met the WAP responder criteria for any given threshold, with greater separation at higher response thresholds.

3.5 | Abdominal discomfort

Abdominal discomfort was also measured as a separate endpoint in the IBS-3001 and IBS-3002 trials, in line with the then-current Rome III IBS diagnostic criteria (now superseded by Rome IV). Interestingly, a significantly greater number of patients in the eluxadoline 100 mg treatment arm met the abdominal discomfort responder criteria of ≥30% reduction in worst abdominal discomfort on ≥50% of days (n = 380, 47.1%) compared to placebo (n = 322, 39.8%) [Table S1].

3.6 | WAP response during placebo washout period

During each month in the IBS-3002 trial, a numerically greater, but statistically insignificant, percentage of eluxadoline-treated patients met the ≥30% WAP response criterion, based on the 50% of time rule (Figure 4) [largest difference seen in Month 6: 46.9% for eluxadoline vs 40.6% for placebo]. However, in the 4-week, blinded placebo washout period (Month 7), where both treatment arms received placebo, this effect was no longer observed; the separation between treatment arm WAP response rates fell to 0.3%.

3.7 | WAP responders by baseline pain severity

There were higher proportions of WAP responders in the eluxadoline group compared to the placebo group for all baseline pain severity categories. The differences were not statistically significant for any group for the 30% improvement threshold nor for the 40% and 50% thresholds for moderate (numeric rating scale [NRS] score 5–<8) or severe (NRS score ≥8) baseline pain categories (Figure 5). However, a significant difference between treatment groups was observed for the overall populations in the 40% and 50% threshold groups (P = .008 and P = .009, respectively), as well as in patients

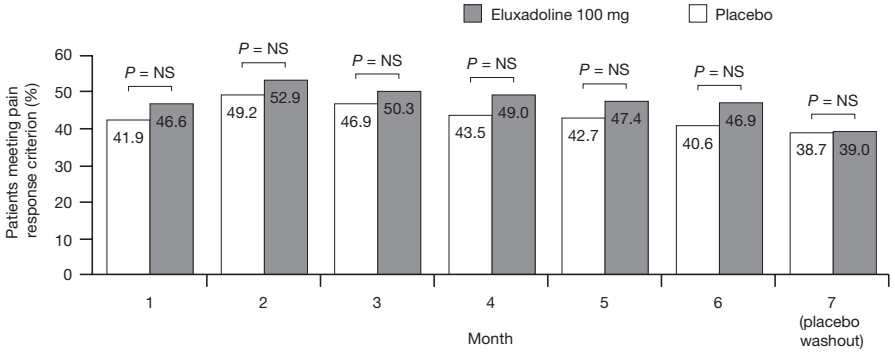

FIGURE 4 Proportions of WAP responders by month (IBS-3002 only), including the placebo washout period (Month 7). NS, not significant; WAP, worst abdominal pain

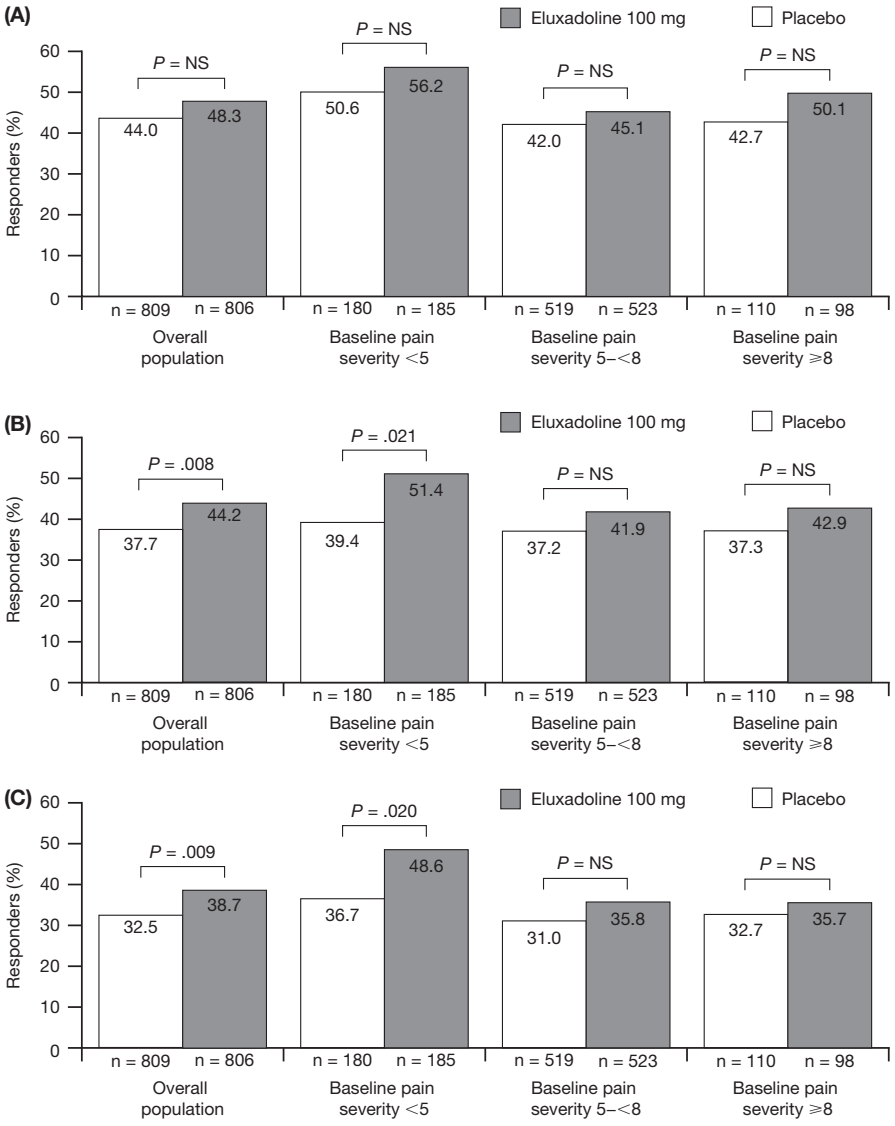

FIGURE 5 Percentage of abdominal pain responders according to baseline pain severity score for response thresholds of (A) 30%, (B) 40%, and (C) 50% improvement in WAP. NS, not significant; WAP, worst abdominal pain

with mild (NRS score <5) baseline pain for both the 40% and 50% thresholds ($P = .021$ and $P = .020$, respectively).

3.8 | WAP responders by different baseline periods

When the baseline WAP score was calculated using data from days −14 to −1 and −21 to −1, rather than days −7 to −1 (data not shown), the percentage of placebo-treated patients subsequently meeting the WAP responder criteria decreased slightly, and the difference between the eluxadoline and placebo groups increased by approximately 1 percentage point. While this approach meant that the effect of eluxadoline achieved statistical significance ($P < .05$), the negligible increase in separation compared to the prespecified baseline calculation used (days −7 to −1) suggests that in these trials, the baseline score calculation period did not greatly affect the findings.

4 | DISCUSSION

Abdominal pain is an important target of any new IBS-D treatment and, as such, assessment of abdominal pain response should be performed across a range of measures. Acknowledging that the magnitude of the difference from placebo is modest, results from these multiple analyses demonstrate that eluxadoline reduces pain compared to placebo, whether this is statistically significant or numerically consistent. In particular, this pooled analysis of Phase 3 trials showed that eluxadoline 100 mg twice daily demonstrated a rapid onset of response in improving WAP scores and continued separation of the eluxadoline and placebo curves throughout the treatment duration, in terms of both daily WAP scores and the percentage of patients meeting different thresholds for WAP response. This effect is further supported by the loss of WAP response observed during the blinded placebo washout period in IBS-3002.

It is worth noting that more than 40% of placebo-treated patients achieved the prespecified WAP responder criteria over the 26-week treatment period. The high placebo response in these trials may partly explain the modest treatment effect observed. A high placebo effect is a common occurrence in IBS trials, and is recognized as a major reason for the large number of late-stage failures seen historically in the development of new IBS treatments.[20] Interestingly, patients with IBS have even been shown to respond to placebo in an unblinded setting.[21,22]

The reasons for the high placebo responses in this and other IBS-D trials are not understood and are likely to involve multiple factors. IBS-D is associated with psychiatric comorbidities and somatization, therefore a positive patient-practitioner relationship may have a profound effect on the measurement of patient-reported outcomes such as pain.[23] In this clinical trial setting, the placebo effect may be heightened by both the discontinuation of IBS-D medications during the screening period, potentially increasing the perception of pain followed by a perceived sense of relief upon blinded study drug initiation, as well as the daily pain assessments which could have improved pain perception through a similar mechanism to that observed in response to a patient-practitioner relationship. In future clinical trials, employing a single-blind placebo run-in period between screening and treatment start may mitigate this effect. Several other tactics for improving IBS clinical trial design have also been suggested, such as including a third "no treatment" arm.[13]

Interestingly, the actual WAP response rates observed for eluxadoline in IBS-D were similar to those seen for linaclotide in IBS-C trials, although the placebo response was notably lower in the linaclotide trials.[24-26]

A further reason for the apparently small effect size may relate to challenges faced in the measurement of abdominal pain in IBS-D trials. Pain is a multifaceted symptom for which frequency and predictability, as well as intensity, are important considerations. While applying the 50% of time rule with a specified pain intensity improvement as a responder criterion helps to account for this,[12] assessing pain response in IBS-D trials remains challenging. The self-reported nature of WAP may be subject to variability over time; patients may adapt to a less painful reality with treatment and thus tend to overrate milder pain, or they may be unduly reliant on the most recent pain experience when reporting once daily, thereby over- or underestimating their true experience. While Ballou et al[27] demonstrated that baseline pain variability was a predictor of WAP placebo response in IBS-C patients, our analyses (using a logistic regression model including baseline WAP standard deviation by treatment interaction term, noting that the WAP responder definition is a function of baseline) in patients with IBS-D failed to demonstrate any predictive capability of baseline pain variability for WAP responder rates (data not shown).

WAP was advocated as the most appropriate measure for abdominal symptoms by the FDA, due to the expectation that pain is experienced with more significant intensity than discomfort,[28] but it is worth noting that a significant effect for eluxadoline was observed for abdominal discomfort.

In the FDA guidance, the ≥30% improvement in WAP was proposed based on experience with other chronic pain conditions. This value has not been fully validated in an IBS population with respect to the method of data collection in this study; however, Spiegel et al (2009)[29] found that the mean clinically important difference using a 10-point NRS to measure abdominal pain in IBS was 2.2 points, corresponding to a 29.5% reduction in abdominal pain. In comparison with our analyses, Spiegel et al used registry rather than clinical trial data, a 10-point scale rather than an 11-point scale, no averaging of baseline pain, and most importantly, no collection of daily pain scores. Despite substantial differences in methodology, Lembo et al documented an average reduction of 3.0 vs 2.6 points (eluxadoline 100 mg vs placebo) in Phase 3 trials (raw scores, pooled data, non-dichotomous).[17]

Additional analyses at higher WAP response thresholds (eg, 40% or 50% improvement) were also prospectively recommended.[28] It is interesting to note that the ≥30% daily WAP response criterion was met by more than half of all placebo patients on every study day after approximately 5-6 weeks of treatment. This suggests that the 30% threshold may not be the most appropriate for the studied population. Indeed, at thresholds of 40% or 50% reduction in WAP on ≥50% of days, the benefit of eluxadoline compared to placebo was statistically significant. Future studies should seek both to replicate and to validate a higher WAP improvement threshold for patients with IBS-D.

While patient-reported severity of IBS-D at baseline (mean severity score calculated over the week preceding randomization) did not have a significant effect on the WAP response to eluxadoline at the 30% improvement threshold, the proportions of WAP responders were clearly and consistently higher for the eluxadoline group compared to the placebo group for all severity categories.[30] Those with mild pain were significantly more likely to achieve a ≥40% or ≥50% improvement in WAP with eluxadoline compared to placebo.

In the eluxadoline trials, a 2- to 3-week screening period was required, with the average of the WAP scores in the final week prior to randomization (days −7 to −1) calculated to obtain the baseline value. When the baseline WAP score was calculated using a longer baseline

period, there was a slight increase in the difference between the eluxadoline and placebo groups, resulting in statistical significance. This negligible increase in separation compared to the prespecified calculation using days −7 to −1 may be serendipitous, but suggests that baseline intervals of at least 14 days may be important in assessing pain differences in IBS-D.

Importantly in the context of other medications used to treat pain, eluxadoline demonstrates activity at the μ- and κ-opioid receptors, leading to potential concerns regarding its abuse liability. However, at doses used in clinical trials for up to 1 year, no evidence of abuse potential or dependence has been observed.[31]

These data should be viewed in light of statistical limitations. While post hoc analyses are a useful tool for conducting a detailed analysis of a specific clinical trial endpoint, they can produce random results falsely interpreted as valuable information. It should also be noted that despite some statistically significant findings, the effect sizes were generally small. Additionally, no statistical adjustments were made a priori to allow for more than two analyses (ie, based on the two doses in the clinical trial).

The chronic and unpredictable nature of IBS-D, with its wide variations in symptom severity, means that a reliable and sustained reduction in abdominal pain is pivotal to achieving effective long-term management of the condition. In this pooled analysis of clinical trials, eluxadoline provided a consistent, clinically meaningful improvement in abdominal pain in patients with IBS-D.

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AUTHOR CONTRIBUTION

PSC, LSD, and DAA contributed to the study design, acquisition, evaluation, and interpretation of the data; AJL contributed to the evaluation and interpretation of the data. All authors had complete access to the data that support the publication.

DISCLOSURES

Financial arrangements of the authors with companies whose products may be related to the present report are listed below, as declared by the authors. Anthony J. Lembo has served as a consultant to Allergan plc, Alkermes, AstraZeneca, Forest Laboratories, Ironwood Pharmaceuticals, Prometheus Laboratories, Salix Pharmaceuticals, and Bausch Health (formerly Valeant Pharmaceuticals). Paul S. Covington has served as a scientific consultant for Allergan plc. Leonard S. Dove serves as a scientific consultant for Allergan plc. David A. Andrae is a former employee of Allergan plc. Some data were presented previously at Digestive Disease Week®, Washington DC in 2015.[18]

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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