Improved work productivity and health-related quality of life in patients with irritable bowel syndrome with diarrhea receiving eluxadoline following inadequate response to loperamide

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What is already known about this subject

- Irritable bowel syndrome with diarrhea (IBS-D) is characterized by recurrent symptoms of abdominal pain and diarrhea that negatively affect work productivity and health-related quality of life (HRQOL).
- Eluxadoline is an efficacious and safe treatment for patients with IBS-D, including those with previous inadequate response to loperamide.

What this study adds

- Treatment with eluxadoline was associated with significant reductions in absenteeism and the number of unhealthy days experienced by patients with IBS-D reporting an inadequate response to loperamide.
- Effective IBS-D therapies, such as eluxadoline, may provide significant cost savings for employers and payers by avoiding work productivity losses and yielding improvements in HRQOL.

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ABSTRACT

BACKGROUND: Irritable bowel syndrome with diarrhea (IBS-D) is a chronic disorder of gut–brain interaction that negatively affects work productivity and health-related quality of life (HRQOL). IBS-D therapeutic options are limited and include loperamide, an over-the-counter μ -opioid receptor agonist commonly used as an antidiarrheal agent, and eluxadoline, a mixed μ - and κ -opioid receptor agonist and δ -opioid receptor antagonist approved in the United States for the treatment of IBS-D in adults.

OBJECTIVE: To characterize the effect of eluxadoline on work productivity and HRQOL in patients with IBS-D with previous inadequate response to loperamide.

METHODS: The Work Productivity and Activity Impairment Questionnaire for IBS-D (WPAI:IBS-D), Centers for Disease Control and Prevention Healthy Days Core Module (CDC HRQOL-4), and EuroQoL-5 Dimension (EQ-5D) instruments were administered at baseline and week 12 of a phase 4 clinical trial (RELIEF), assessing the efficacy and safety of eluxadoline treatment in adults with IBS-D reporting previous inadequate response to loperamide. Changes from baseline to week 12 for each assessment were evaluated using an analysis of covariance model. Indirect costs were calculated by converting overall work productivity losses into monetary values.

RESULTS: A total of 346 patients were randomized to either eluxadoline ($n=172$) or placebo ($n=174$). From baseline to week 12, compared with placebo, twice-daily treatment with eluxadoline resulted in significantly greater reductions in absenteeism (2.6%; $P=0.046$). Numerically greater decreases in presenteeism, overall work productivity loss, and daily activity impairment were also observed in patients receiving eluxadoline compared with those receiving placebo (P = not significant for each). Numerical reductions in overall work productivity loss from baseline to week 12 translate to approximately 2.4 hours per patient per week (123 hours annually) and correspond to an avoided overall work loss of \$4,503 annually for an employee with IBS-D treated with

eluxadoline. In addition, from baseline to week 12, treatment with eluxadoline led to a significantly greater reduction in the number of unhealthy days experienced (-1.7 days; $P=0.042$), as well as numerical improvements in EQ-5D measures in comparison with placebo (P =not significant for each).

CONCLUSIONS: In patients with IBS-D reporting inadequate response to loperamide, eluxadoline treatment was associated with significant reductions in absenteeism and the number of unhealthy days experienced. Eluxadoline treatment of IBS-D may lead to significant cost savings via mitigation of losses in work productivity.

Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction characterized by symptoms of recurrent abdominal pain and altered bowel habits.^{1,2} IBS with diarrhea (IBS-D) is a subtype of IBS, wherein patients report more frequent mushy or watery stools in association with their abdominal pain.^{1,2} IBS is highly prevalent in the United States; it is estimated that the disorder affects 1 in 9 adults, and up to 40% of IBS patients present with the diarrhea-predominant stool subtype.³

The recurrent abdominal and bowel symptoms associated with IBS-D are debilitating and have been shown to negatively affect health-related quality of life (HRQOL) and work productivity. Patients with IBS-D report reduced HRQOL compared with healthy individuals without IBS⁴⁻⁶ and generally suffer greater effects on HRQOL relative to other IBS subtypes.⁷ Reductions in work productivity, characterized by absenteeism (i.e., missed days of work), presenteeism (i.e., impairment in productivity while at work), overall work productivity loss, and impairments in daily activities, have also been reported in patients with IBS-D.^{4,8} Notably, patients affected by severe IBS symptoms report even greater impairments in work and daily activities and lower labor force participation.⁸ Overall work productivity loss has been estimated to result in indirect costs of \$2,486 per year (in 2012 U.S. dollars [USD]) for adults with IBS D versus those without.⁴ Together, these findings highlight the significant psychosocial and economic burden of illness for patients with this disorder.

Eluxadoline, a mixed μ -opioid and κ -opioid receptor agonist and δ -opioid receptor antagonist, was approved in 2015 for the treatment of adults with IBS-D in the United States.⁹ In 2 randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical trials, eluxadoline was found to be safe and efficacious in treating patients with IBS-D, resulting in significant improvements in abdominal and bowel symptoms.¹⁰⁻¹² In a pooled analysis of both trials, treatment with eluxadoline was shown to significantly

improve HRQOL from baseline to week 26 compared with placebo.¹³ Improvements in HRQOL were detected within 4 weeks of initiating eluxadoline and were sustained over 1 year.¹³

More recently, eluxadoline demonstrated efficacy in a phase 4 clinical trial (RELIEF; NCT02959983) that involved 346 patients with IBS-D who reported previous inadequate response to loperamide; a significantly greater proportion of patients treated with eluxadoline achieved the composite responder endpoint compared with placebo (22.7% vs. 10.3%, respectively). The composite responder endpoint was defined by an improvement of $\geq 40\%$ in worst abdominal pain in the preceding 24 hours, and a Bristol Stool Form Scale score of < 5 for at least 50% of treatment days.¹⁴ Loperamide, a μ -opioid receptor agonist, is the most commonly prescribed treatment for diarrhea; however, many patients with IBS-D experience inadequate response to this agent.^{15,16} In a post hoc analysis of phase 3 clinical trials for eluxadoline, 36.0% of patients reported previous loperamide use, and of those patients, 61.8% reported inadequate control of IBS-D symptoms with loperamide.¹⁶

The effect of eluxadoline treatment on work productivity and HRQOL has not heretofore been examined in patients with IBS-D reporting inadequate response to loperamide. Thus, a greater understanding of this interplay, and the indirect costs associated with this disorder, may be important for health care decision making. The objective of this study was to assess the effect of eluxadoline on work productivity and HRQOL in adults with IBS-D who reported previous inadequate response to loperamide, using data from the RELIEF study.

Methods

PATIENT POPULATION AND STUDY DESIGN

Data on work productivity and HRQOL were obtained from the randomized, double-blind, placebo-controlled, parallel-group, phase 4 RELIEF trial. Details relating to the study design, study sample attrition, and clinical results have been reported in detail previously.¹⁴ Briefly, adults aged 18-80 years were eligible to participate if they met Rome III criteria for IBS-D and reported the following¹⁷: (1) mean worst abdominal pain scores > 3.0 (11-point scale; 0 = no pain, 10 = worst imaginable pain); (2) mean Bristol Stool Form Scale scores ≥ 5.5 (7-point scale; 1 = hard stool, 7 = watery diarrhea) for ≥ 5 days in the preceding 2 weeks; (3) use of loperamide within the 12 months before study enrollment with a subjective lack of adequate control of IBS-D symptoms; and (4) no loperamide rescue medication use within the 2 weeks before randomization. Exclusion criteria included history

of cholecystectomy; comorbid inflammatory bowel disease; celiac disease; intestinal obstruction; history of alcohol use disorders (i.e., recurring harmful use of ethanol); pancreatitis; or sphincter of Oddi dysfunction.¹⁴ The study protocol and other relevant documentation were approved by the institutional review board at each study site. All patients provided written, informed consent before study procedures were initiated. Patient confidentiality was protected, in line with Good Clinical Practice and the Declaration of Helsinki.

Eligible patients were randomized to receive oral eluxadoline (100 mg) or placebo twice daily for 12 weeks.¹⁴ Health outcomes assessments, including an IBS-D-specific Work Productivity and Activity Impairment (WPAI:IBS-D) questionnaire,^{18,19} the Centers for Disease Control and Prevention Healthy Days Core Module (CDC HRQOL-4),²⁰ and the EuroQoL-5 Dimension (EQ-5D) instrument,²¹ were administered to patients at baseline, week 4, week 8, and at the end of the 12-week treatment period. The current analyses present changes in WPAI:IBS-D, CDC HRQOL-4, and EQ-5D scores from baseline to week 12, since trajectories over time for these measures did not differ within or between groups at weeks 4 and 8 (data not shown).

WORK PRODUCTIVITY AND HRQOL ASSESSMENTS

WPAI:IBS-D. The WPAI is a self-administered questionnaire consisting of 6 items intended to assess work productivity and daily activity impairment due to a particular health problem in the preceding 7 days.^{18,19} The reliability and validity of the WPAI in patients with IBS (WPAI:IBS) have been previously reported.¹⁹ The WPAI:IBS was modified for use in patients with IBS-D in the RELIEF study by removing “constipation” from the description of symptoms related to IBS to ensure that the questionnaire was specific to the study population (WPAI:IBS-D). The WPAI:IBS D measures 4 domains; scores for each domain were defined and calculated at baseline and week 12 as follows:

1. Absenteeism (work hours missed due to IBS-D), calculated as $[\text{hours missed due to IBS-D} \div (\text{hours missed due to IBS-D} + \text{hours worked})] \times 100$
2. Presenteeism (degree to which symptoms of IBS-D affect productivity while at work), calculated as $[\text{degree that IBS-D affected productivity while working} \div 10] \times 100$
3. Overall work productivity loss (absenteeism plus presenteeism due to IBS-D), calculated as $[(\text{absenteeism}) + (\text{hours worked} \times \text{presenteeism})] \times 100$
4. Daily activity impairment (degree to which IBS-D symptoms affect regular activities, e.g., housework, shopping, childcare, exercising, and studying), calculated as $[\text{degree that health affected daily activities} \div 10] \times 100$

WPAI:IBS-D scores are represented as percentages (range of 0%-100%), with higher percentages indicating greater work productivity loss and daily activity impairment.

CDC HRQOL-4. The CDC HRQOL-4 is used to evaluate perceived physical and mental health during the preceding 30 days; it has been validated across populations and has demonstrated utility in distinguishing between different disease states.²⁰ Responses are reported as a summary index of the number of unhealthy days (calculated as days of poor physical health + days of poor mental health), wherein lower numbers indicate better quality of life, based on CDC guidance for the analysis of this measure.²⁰

EQ-5D. The EQ-5D instrument is a short, preference-based measure of health status commonly used to measure HRQOL for the economic evaluation of health care interventions. The reliability and validity of the EQ-5D in patients with IBS has been previously reported.²² Patients with IBS-D were asked to complete the descriptive system (scale of -0.594 to 1.000; 1=perfect health, 0=death; negative values are valued as worse than death) and visual analog scale (scale of 0 to 100; 0=worst health, 100=best health) of this instrument at baseline and week 12. The descriptive system included 5 questions assessing the following domains: (1) mobility, (2) self-care, (3) usual activities, (4) pain/discomfort, and (5) anxiety/depression.²¹ U.S.-specific preference weights were used to transform responses to the 5 questions into utility values.²³

STATISTICAL ANALYSES

The phase 4 RELIEF trial had a planned enrollment of 340 patients (i.e., 170 patients per arm). This sample size provided approximately 90% power to detect the difference in the primary composite responder endpoint response for eluxadoline versus placebo using a two-sided chi-square test at a significance level of $\alpha=0.05$. Sample size calculations for secondary endpoints, including measures of work productivity and HRQOL, were not considered a priori.

Analyses of the WPAI:IBS-D, CDC HRQOL-4, and EQ-5D measures were based on the intent-to-treat (ITT) population; patients included in the analyses of changes from baseline completed baseline and week 12 assessments. Mean scores for absenteeism, presenteeism, and overall work productivity loss were calculated for employed patients only (i.e., 41.9% of patients who completed at least 1 of the measures). Mean scores for daily activity impairment were calculated for all patients in the ITT population, regardless of employment status.

Descriptive statistics were tabulated for demographics, clinical characteristics, and mean scores on the WPAI:IBS-D, CDC HRQOL-4, and EQ-5D. Significance tests

TABLE 1 Demographics, Clinical Characteristics, and Baseline Scores on the WPAI:IBS-D, CDC HRQOL-4, and EQ-5D

	Placebo (n=174)	Eluxadoline (n=172)
Age, years, mean $\pm$ SD	43.9 $\pm$ 14.2	43.8 $\pm$ 13.9
Female, n (%)	119 (68.4)	124 (72.1)
Caucasian, n (%)	141 (81.0)	144 (83.7)
Not Hispanic or Latino, n (%)	133 (76.4)	139 (80.8)
Symptom scores, mean $\pm$ SD		
Daily worst abdominal pain	6.0 $\pm$ 1.6	6.3 $\pm$ 1.5
Daily abdominal discomfort	6.2 $\pm$ 1.6	6.4 $\pm$ 1.5
Daily abdominal bloating	6.2 $\pm$ 1.9	6.5 $\pm$ 1.6
Daily number of bowel movements	4.2 $\pm$ 2.3	4.0 $\pm$ 1.8
Daily number of urgency episodes	2.9 $\pm$ 2.4	2.7 $\pm$ 1.8
Daily number of bowel incontinence episodes	1.1 $\pm$ 2.0	1.2 $\pm$ 2.0
Weekly incontinence-free days	5.3 $\pm$ 1.8	5.2 $\pm$ 1.8
Duration of IBS-D, years	10.3 $\pm$ 10.8	9.5 $\pm$ 10.0
WPAI:IBS-D scores, mean $\pm$ SD		
Absenteeism, % ^a	7.8 $\pm$ 15.6	7.7 $\pm$ 16.7
Presenteeism, % ^b	44.4 $\pm$ 23.4	50.0 $\pm$ 23.3
Overall work productivity loss, % ^b	47.0 $\pm$ 25.4	52.5 $\pm$ 24.1
Daily activity impairment, % ^c	45.8 $\pm$ 23.2	52.0 $\pm$ 23.2
CDC HRQOL-4 scores		
Number of unhealthy days ^d	6.2 $\pm$ 8.9	7.2 $\pm$ 9.8
EQ-5D scores		
Utility score ^c	0.833 $\pm$ 0.157	0.818 $\pm$ 0.155
Visual analog scale score ^c	81.197 $\pm$ 13.277	81.089 $\pm$ 15.582

Note: Sample sizes vary as a result of missing data due to patients not completing all WPAI:IBS-D, CDC HRQOL-4, and EQ-5D measures at all visits.

^an=78 (placebo; 45%) and n=67 (eluxadoline; 39%) for absenteeism.

^bn=78 (placebo; 45%) and n=66 (eluxadoline; 38%) for presenteeism and overall work productivity loss.

^cn=132 (placebo; 76%) and n=123 (eluxadoline; 72%) for daily activity impairment and EQ 5D scores.

^dn=124 (placebo; 71%) and n=119 (eluxadoline; 69%) for the CDC HRQOL-4.

CDC HRQOL-4=Centers for Disease Control and Prevention Healthy Days Core Module; EQ-5D=EuroQoL-5 Dimension; IBS-D=irritable bowel syndrome with diarrhea; WPAI:IBS-D=Work Productivity and Activity Impairment Questionnaire for IBS-D.

were not performed for baseline differences, in line with guidance for randomized clinical trials from the Consolidated Standards of Reporting Trials Statement.²⁴

Changes from baseline to week 12 in WPAI:IBS-D, CDC HRQOL-4, and EQ-5D scores were analyzed using an analysis of covariance model, with the

baseline score as a covariate and the treatment group and country of study site as fixed effects; least squares mean change from baseline to week 12 values are presented herein. Treatment effects were measured as the least squares mean difference between eluxadoline and placebo based on the results of the analysis of covariance.

All treatment comparisons were performed with two-sided tests and at a nominal significance level of $P < 0.05$. Here, the term “numerical” is used to denote nonstatistically significant changes.

The mean number of work hours lost as a result of overall work productivity loss was estimated by assuming full-time employment of 40 hours per week (2,080 hours of potential work-time annually) per employed patient. Overall work productivity losses were converted into monetary values using the human capital cost approach,²⁵ by multiplying the total number of hours lost by the average hourly employment cost of a U.S. employee (\$36.61 as of June 2019, comprising an average hourly wage of \$25.12 and average benefits of \$11.48).²⁶ All assumed costs are reported in 2019 USD.

Results

DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

A total of 346 patients with IBS-D were randomized to either eluxadoline (n=172) or placebo (n=174). Baseline characteristics were comparable between treatment groups (Table 1); the mean age was approximately 43.8 years and the majority of patients were female (70.2%) and White (82.4%). Patients with IBS-D reported a mean disease duration of 9.9 years. Work and HRQOL data were available for the subset of patients who responded to the health outcomes assessments at baseline and week 12 (Table 1).

WORK PRODUCTIVITY AND DAILY ACTIVITY IMPAIRMENT

At baseline, mean rates of absenteeism were comparable between treatment groups (eluxadoline vs. placebo: 7.7% vs. 7.8%), whereas mean rates of presenteeism (50.0% vs. 44.4%), overall work productivity loss (52.5%

FIGURE 1**Mean Changes from Baseline to Week 12 in Absenteeism, Presenteeism, Overall Work Productivity Loss, and Daily Activity Impairment in the Eluxadoline and Placebo Groups**

Note: Data are presented as mean score $\pm$ standard error of mean at baseline and week 12, with the LS mean change between time points calculated in patients with baseline assessments.

^aA significant LS mean difference between groups, $P \leq 0.05$. Sample sizes vary from baseline to week 12 due to missing data for patients who did not complete the WPAI:IBS-D assessment at all study visits. Sample sizes also vary across domains, since mean scores for absenteeism, presenteeism, and overall work productivity loss were calculated for employed patients only.

^bA significant LS mean change within groups from baseline to week 12, $P < 0.05$. The LS mean difference between groups, for change from baseline to week 12, is also shown.

IBS-D = irritable bowel syndrome with diarrhea; LS = least squares; WPAI:IBS-D = Work Productivity and Activity Impairment Questionnaire for IBS-D.

vs. 47.0%), and daily activity impairment (52.0% vs. 45.8%) were numerically higher in the eluxadoline-treated group (Table 1). Changes from baseline to week 12 in the WPAI:IBS-D domains are shown by treatment group in Figure 1. From baseline to week 12, treatment with eluxadoline was associated with a significant reduction of 2.6% for absenteeism (95% CI = -5.2-0.0; $P = 0.046$). Numerical reductions of 4.8% for presenteeism (95% CI = -12.1-2.5; $P = \text{NS}$), 5.9% for overall work productivity loss (95% CI = -13.6-1.7; $P = \text{NS}$), and 3.4% for daily activity impairment (95% CI = -8.9-2.0; $P = \text{NS}$) were also observed for eluxadoline compared with placebo, but these changes were not statistically significant (Figure 1).

INDIRECT COSTS

Based on the treatment effect of eluxadoline versus placebo (i.e., for absenteeism: -2.6%) and an assumed 40-hour work week, treatment with eluxadoline reduced overall work productivity loss (absenteeism plus presenteeism) by 2.4 hours per patient per week (i.e., overall work productivity loss [5.9%] $\times$ 40 hours per week = approximately 2.4 hours per patient per week, or 123 hours per patient annually) at week 12. These hours translate to indirect costs of \$4,503 per patient per year, which could be potentially avoided with effective IBS-D treatment.^{25,26}

FIGURE 2 Mean Changes from Baseline to Week 12 in the Number of Unhealthy Days During the Last 30 Days in the Eluxadoline and Placebo Groups

Note: Data are presented as mean number of unhealthy days $\pm$ standard error of mean at baseline and week 12, with the LS mean change between time points.

^aA significant LS mean difference between groups, $P \leq 0.05$.

^bA significant LS mean change within groups from baseline to week 12, $P < 0.05$. The LS mean difference between groups, for change from baseline to week 12, is also shown.

^cSample sizes for the CDC HRQOL-4 were the same at baseline as week 12. CDC HRQOL-4 = Centers for Disease Control and Prevention Healthy Days Core Module; LS = least squares.

CDC HRQOL-4

At baseline, mean numbers of unhealthy days were numerically higher among patients in the eluxadoline treatment group compared with patients in the placebo group (7.2 days vs. 6.2 days; Table 1). From baseline to week 12, treatment with eluxadoline significantly reduced the number of unhealthy days reported in the preceding 30 days by 1.7 days compared with placebo (95% CI = -3.4, -0.1; $P = 0.042$; Figure 2). This reduction translates to an additional 20.4 healthy days per year (i.e., 1.7 days $\div$ month $\times$ 12 months), which could be gained with eluxadoline treatment.

EQ-5D

At baseline, patients in the eluxadoline and placebo groups had comparable mean utility (0.818 vs. 0.833) and visual analog scale scores (81.089 vs. 81.197) on the EQ-5D (Table 1). Changes from baseline to Week 12 in these measures are shown by treatment group in Figure 3. From baseline to week 12, treatment with eluxadoline was associated with numerical improvements of 0.014 units in EQ-5D utility scores ($P = \text{NS}$) and 1.452 units in visual analog scale scores ($P = \text{NS}$) compared with placebo.

Discussion

Previous studies have highlighted the substantial physical, psychosocial, and economic burden experienced by patients with IBS-D.^{4,7} Indeed, patients with IBS-D have reported experiencing gastrointestinal symptoms, including diarrhea, abdominal pain, bloating, and urgency, that are extremely or very bothersome, on at least 4 to 6 days of the week.²⁷ Because these recurrent symptoms have been linked to reduced work productivity⁴ and HRQOL,^{4,7} understanding the effects of IBS-D treatments, such as eluxadoline, on work productivity and HRQOL may be beneficial to employers and health care decision makers.

In the phase 4 RELIEF study of eluxadoline in patients with IBS-D reporting previous inadequate responses to loperamide, a significantly greater proportion of patients treated with eluxadoline achieved the composite responder endpoint compared with the placebo group.¹⁴ While these endpoints were important to the demonstration of clinical efficacy, the current study reports the effects of eluxadoline on work productivity and HRQOL, secondary endpoints that may be very important and reflect the indirect burden of the disorder on the affected individual.

Baseline WPAI:IBS-D scores reported in the current study are slightly higher than the WPAI:General Health scores previously reported in adults with IBS-D.⁴ This is not entirely surprising, given that the 2 studies used different versions of the WPAI in 2 different patient populations. The study population in the recent publication by Buono et al. (2017) was identified from a national survey based on self-reported diagnoses of IBS-D, with only 33.8% of respondents reporting ongoing use of over-the-counter therapies for IBS-D and less than half (43.6%) taking loperamide.⁴ Conversely, all patients in the RELIEF study population had confirmed diagnoses of IBS-D and reported persistence of diarrhea and abdominal pain symptoms on loperamide. Accordingly, patients in the current study may have greater IBS-D severity, resulting in higher baseline

FIGURE 3 Mean Changes from Baseline to Week 12 in EQ-5D Utility (A) and Visual Analog Scale Scores (B) in the Eluxadoline and Placebo Groups**A. Mean Changes in EQ-5D Utility** **B. Visual Analog Scale Scores**

Note: Data are presented as mean score $\pm$ standard error of mean at baseline and week 12, with the mean change between time points. The LS mean difference between groups, for change from baseline to Week 12, is shown. Nonsignificant mean changes were observed within groups and between groups from baseline to week 12, $P \geq 0.10$.

^aSample sizes for the EQ-5D were the same at baseline as week 12.

EQ-5D = EuroQoL-5 Dimension; LS = least squares.

disruptions in work productivity than the general population of patients with IBS-D.

Treatment with eluxadoline significantly reduced absenteeism by 2.6% from baseline to week 12 compared with placebo. Numerical reductions were also observed in favor of eluxadoline for presenteeism, overall work productivity loss, and daily activity impairment. The observed reductions within the eluxadoline-treated population were within the proposed clinically meaningful range for the WPAI but did not reach statistical significance.²⁸ The estimated cost savings associated with eluxadoline treatment suggests that the economic burden of IBS-D stemming from indirect costs may be lessened with appropriate treatment of abdominal pain and diarrhea symptoms. It could also be surmised that, in some cases, the cost savings may offset the increased medical expenses associated with IBS-D or

may even exceed the retail costs of eluxadoline.²⁹ However, the estimated cost savings due to eluxadoline suggested in this study remain speculative and require further validation, since this calculation was based on numerical reductions in presenteeism and assumed full-time employment.

Treatment with eluxadoline also significantly reduced the number of unhealthy days reported by patients with IBS-D in the preceding 30 days compared with placebo (least squares mean difference = -1.7 days; 95% CI = -3.4, -0.1; $P = 0.042$). Because a 1-day change in unhealthy days is generally thought to be clinically meaningful on the CDC HRQOL-4,²⁰ this result demonstrates the positive effect of eluxadoline on HRQOL, consistent with previous findings of clinical improvement with eluxadoline in phase 3 clinical trials.^{10,11,13}

Patients in the eluxadoline group had numerically greater increases in EQ-5D utility scores from baseline to week 12 compared with patients in the placebo group (least squares mean difference=0.014; $P=NS$). As with the WPAI:IBS-D, changes observed in utility scores during the treatment period in both groups were within the proposed clinically meaningful range for the EQ-5D (-0.011 units to 0.140 units).³⁰ The placebo responses in the current analysis are similar to those reported in previous trials in IBS-D.^{10,11,31,32} Although treatment differences for the HRQOL endpoints were small, the global improvement in abdominal pain and bowel symptoms is still viewed to be preferable to placebo in patients both naive to and previously failing loperamide.^{10,14} Together, these numerical improvements with eluxadoline and high concurrent placebo effects observed underscore the strong psychosocial underpinnings of effective treatments for IBS D in patients who have failed loperamide, the most commonly used treatment in this patient population.

A recent nationwide survey found that most patients with IBS feel self-conscious when their diarrhea symptoms emerge and are embarrassed when others notice that they are frequently in the bathroom; patients might therefore opt to stay home from work when symptoms are active.²⁷ The improvements in work productivity and HRQOL observed in this analysis may reflect the efficacy of eluxadoline in alleviating diarrhea and abdominal pain,¹⁴ since abdominal pain management has been identified as a predictor of improvements in HRQOL for pharmacologic treatment of IBS.³³ Ultimately, improvements in diarrhea and abdominal pain may reduce the likelihood that a patient will feel compelled to take sick leave due to IBS-D symptoms, thereby decreasing absenteeism and the

number of unhealthy days experienced and improving overall HRQOL.

LIMITATIONS

The results of the current analysis should be interpreted in light of certain limitations. First, the RELIEF study was restricted to patients with previous inadequate response to loperamide, perhaps suggesting greater baseline disruptions and severity of IBS-D and limiting the generalizability of these findings to IBS-D at large.

Second, by design, the study was not undertaken with sufficient a priori power to detect changes in the secondary endpoints, including the work productivity and HRQOL measures; hence, sample sizes should be taken into consideration when interpreting the data.

Further, responses on health outcomes assessments were not available for approximately one quarter of the ITT population, which should be considered when interpreting the effects of eluxadoline on work productivity and HRQOL. Nevertheless, the proportion of patients with missing data was similar for the eluxadoline and placebo groups.

Conclusions

IBS-D is a burdensome illness that affects work productivity and HRQOL, particularly among potentially more severe patients who have failed previous therapies. This phase 4 clinical trial in patients with IBS-D reporting inadequate response to loperamide suggests that, compared with placebo, twice-daily treatment with eluxadoline may significantly reduce absenteeism and the number of unhealthy days experienced. Numerical improvements were observed in presenteeism, overall work productivity loss, and daily activity impairment. These observations may be due, in part, to the effect of eluxadoline on the bothersome

abdominal and bowel symptoms of IBS-D.¹⁴ Eluxadoline's potential to mitigate losses in work productivity may translate into cost savings for employers and hence should be of considerable interest to health care decision makers.

DISCLOSURES

This study was sponsored by Allergan plc (before acquisition by AbbVie, Inc.). Allergan plc and/or AbbVie, Inc., was involved in the study design, collection, analysis, interpretation of the data, writing of the report, and the decision to submit the report for publication. Abel and Burslem are employees of AbbVie, Inc., and own stock/stock options. Brenner has served as a consultant, speaker, and/or advisor for Allergan plc (before acquisition by AbbVie, Inc.), Alnylam, Alpha Sigma, Arena, Bayer, Ironwood Pharmaceuticals, Salix Pharmaceuticals, Shire, Synergy, and Takeda Pharmaceuticals. He is also supported in research by an unrestricted gift from the Irene D. Pritzker Foundation. Sayuk has served as a consultant and speaker for Allergan plc (before acquisition by AbbVie, Inc.), Gi Health Foundation, Ironwood Pharmaceuticals, Salix Pharmaceuticals, and Synergy.

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