ORIGINAL RESEARCH

Impact of Linaclotide Treatment on Work Productivity and Activity Impairment in Adults with Irritable Bowel Syndrome with Constipation: Results from 2 Randomized, Double-Blind, Placebo-Controlled Phase 3 Trials

Jessica L. Buono, MPH; Stavros Tourkodimitris, PhD; Phil Sarocco, RPh, MSc; Jeffrey M. Johnston, MD; Robyn T. Carson, MPH

Background: Irritable bowel syndrome with constipation (IBS-C), a chronic functional gastrointestinal disorder, has been shown to negatively affect work productivity and impair daily activity, resulting in a substantial burden for patients and employers. Linaclotide is a first-in-class guanylate cyclase-C agonist approved for the treatment of adults with IBS-C and chronic idiopathic constipation in the United States.

Objective: To analyze the impact of treatment with linaclotide on work productivity and daily activity impairment in adults with IBS-C and estimate the indirect costs associated with this condition.

Methods: This was a post-hoc analysis of data on IBS-C–related work time missed and work and activity impairment from 2 phase 3 clinical trials that assessed the efficacy and safety of linaclotide therapy in adults with IBS-C. The Work Productivity and Activity Impairment Questionnaire for IBS-C (WPAI:IBS-C) was self-administered at baseline and at weeks 4, 8, and 12 during the 12-week treatment periods in Trials 1 and 2 and at weeks 16, 20, and 26 during the extended treatment period in Trial 2. An analysis of covariance was conducted to assess changes from baseline to all study weeks for each WPAI:IBS-C measure. Indirect costs were calculated by converting overall work productivity losses into monetary values using the human capital cost approach.

Results: Of the 1602 patients with IBS-C who were randomized in the 2 clinical trials, 1555 (97.1%) completed a baseline and at least 1 postbaseline WPAI:IBS-C assessment and were included in the analysis cohort; 1148 (71.7%) of these patients were employed. Once-daily treatment with linaclotide significantly reduced overall work productivity loss and daily activity impairment among patients with IBS-C at all study weeks. From baseline to week 12, compared with placebo, linaclotide significantly reduced presenteeism by 5.2%, overall work productivity loss by 6.1%, and daily activity impairment by 4.7% (all P <.01) and led to a numerically greater decrease in absenteeism. From baseline to week 26, compared with placebo, reductions with linaclotide were 5.9% for presenteeism, 7.5% for overall work productivity loss, and 6.7% for daily activity impairment (all P <.05). Reductions in overall work productivity loss from baseline to week 26 translate to 103 hours to 156 hours annually and correspond to an avoided overall work loss of $3209 to $4861 annually for an employee with IBS-C.

Conclusion: The results of this analysis indicate that appropriate treatment of IBS-C with medications such as linaclotide can reduce work-related impairment associated with IBS-C. In addition, IBS-C therapies that effectively manage this chronic condition and improve employees' quality of life and work productivity may represent significant cost-savings for employers in the form of avoided work productivity losses.

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Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterized by recurrent abdominal pain or discomfort accompanied by changes in bowel habits.[1] IBS with constipation (IBS-C) is a subtype of IBS characterized by hard or lumpy stools for ≥25% of bowel movements and loose or watery stools for

Ms Buono is Manager, Health Economics and Outcomes Research, Forest Research Institute, LLC, a subsidiary of Actavis plc, Jersey City, NJ; Dr Tourkodimitris is Director, Biostatistics, Forest Research Institute, LLC, a subsidiary of Actavis plc, Jersey City, NJ; Mr Sarocco was Senior Director, Health Economics and Outcomes Research, Ironwood Pharmaceuticals, Cambridge, MA, during this study; Dr Johnston is Senior Principal Clinical Scientist, Clinical Affairs, Ironwood Pharmaceuticals, Cambridge, MA; and Ms Carson is Director, Health Economics and Outcomes Research, Forest Research Institute, LLC, a subsidiary of Actavis plc, Jersey City, NJ.

KEY POINTS

- Irritable bowel syndrome with constipation (IBS-C) negatively affects work productivity and impairs daily activity, resulting in a substantial burden for patients and employers.
- This is the first study to assess the impact of linaclotide therapy on work productivity and daily activity among patients with IBS-C and to analyze indirect costs associated with this condition.
- Among this study population, an average work productivity loss of 35.1% at baseline translated into a loss of 730 hours, or $22,747 in lost costs, annually, for each employed patient with IBS-C.
- Linaclotide therapy significantly reduced overall work productivity loss and daily activity impairment among patients with IBS-C at all study weeks.
- Therapies for IBS-C that effectively manage this chronic condition and improve work productivity may present opportunities for cost-savings for employers in the form of avoided work losses.

<25% of bowel movements in the absence of an antidiarrheal or laxative use.[1] IBS-C is estimated to affect 1.3% to 5.2% of the adult population in the United States[2-5] and occurs more frequently in women than in men.[6,7] Women have been found to have 1.33 times the odds of IBS compared with men overall,[8] and nearly 2.5 times the odds of having the IBS-C subtype compared with men among patients with IBS.[7,9] The prevalence of IBS has also been found to be highest among younger age-groups; patients aged >60 years have half the odds of having IBS compared with patients aged <40 years.[8] The peak age range for patients who currently have symptoms of IBS was reported to be between 25 and 54 years.[3]

The symptom burden experienced by patients with IBS has been shown to negatively affect their health-related quality of life (HRQOL) and work productivity, and result in significant direct (ie, healthcare resource utilization) and indirect (ie, lost work productivity) costs.[10-16] Although the majority of cost estimates focus on IBS overall rather than specific subtypes of IBS, with the direct cost estimates for inpatient, outpatient, physician, and prescription drug services ranging from $1674 (in 2010 USD) to $1896 (in 2010 USD) per patient annually, IBS-C has been shown to impose a substantial burden in direct healthcare costs for third-party payers, estimated at $3856 (in 2010 USD) in incremental costs per patient with IBS-C annually compared with matched controls in a commercially insured population.[13-17] However, the total costs incurred by employers include the direct costs related to insurance payments for medical care, as well as the indirect costs associated with absenteeism (ie, missed days of work) and presenteeism (ie, impairment in productivity while at work).

Few studies report the indirect costs associated with IBS, and no studies to date have reported the indirect costs specifically for IBS-C. Considering that the majority (approximately 79%) of patients with IBS are of working age, the indirect costs and the associated economic impact on employers could be substantial.[18] The indirect medical costs related to absenteeism have been estimated at approximately $3400 annually (in 2013 USD) for 1 employee with IBS, an excess of approximately $670 compared with the indirect costs of age- and sex-matched controls.[14]

Overall, lost work productivity resulting from absenteeism in patients with IBS has been estimated to result in $27 billion (in 2013 USD) in indirect costs annually for US employers.[18] However, because these estimates only account for costs related to absenteeism, and IBS symptom-related losses in work productivity are predominantly driven by presenteeism rather than absenteeism, it is likely that these costs significantly underestimate the true economic burden of IBS to US employers.[11,14,19-21]

A previous analysis specific to IBS-C based on data from the US National Health and Wellness Survey showed that adults with IBS-C had significantly higher mean levels of presenteeism (31.7% vs 21.4%, respectively), overall work productivity loss (35.5% vs 25.3%, respectively), and daily activity impairment (45.8% vs 33%, respectively) compared with matched controls.[19] This study, however, did not estimate the costs associated with lost work productivity.

Linaclotide, a minimally absorbed guanylate cyclase-C agonist, is a first-in-class therapy approved for the treatment of adults with IBS-C and chronic idiopathic constipation in the United States,[22] and for moderate-to-severe IBS-C in Europe.[23] In 2 randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase 3 clinical trials in adults with IBS-C, treatment with linaclotide was shown to significantly improve abdominal and bowel symptoms.[24,25] The effects of treatment with linaclotide on work productivity and daily activity, however, have not yet been described. The objective of this study was to evaluate the impact of treatment with linaclotide on work productivity and on daily activity impairment in adults with IBS-C using data from these 2 phase 3 clinical trials.

Methods

Patient Population and Study Design

Data on IBS-C–related work time missed and work and activity impairment were evaluated using informa-

tion from 2 randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase 3 IBS-C trials (henceforth, Trial 1 and Trial 2) for which clinical results have been reported previously.[24,25] Briefly, adults meeting modified Rome II criteria[1] for IBS-C were eligible to participate if they had the following symptoms for ≥12 weeks (which need not be consecutive) in the 12 months before the screening visit[24,25]:

- Abdominal pain or abdominal discomfort associated with at least 2 of the following symptoms:
  - Relieved with defecation
  - Onset associated with a change in frequency of stool
  - And/or onset associated with a change in form (appearance) of stool
- Less than 3 spontaneous bowel movements (defined as bowel movements occurring in the absence of laxative, enema, or suppository use during the 24 hours before the bowel movement) weekly
- At least 1 additional bowel symptom (straining, lumpy or hard stools, and sensation of incomplete evacuation during >25% of bowel movements) weekly.

In addition, patients were required to have an average weekly score of ≥3 for daily abdominal pain at its worst (on an 11-point numerical rating scale), as well as <3 complete spontaneous bowel movements (defined as spontaneous bowel movements with a feeling of complete evacuation) and ≤5 spontaneous bowel movements weekly during the 14-day pretreatment period (ie, baseline period).

Eligible patients were randomized to receive an oral capsule of linaclotide 290 µg once daily or placebo for at least 12 weeks. Trial 1 included a 12-week treatment period, with an additional 4-week randomized withdrawal period,[24] whereas Trial 2 featured a treatment period of 26 weeks.[25] In both trials, the primary efficacy end points were assessed over the initial 12 weeks of treatment.[24,25]

Work Productivity and Activity Impairment Questionnaire

The Work Productivity and Activity Impairment (WPAI) questionnaire is a self-administered questionnaire consisting of 6 items intended to assess work time missed and work and activity impairment during the past 7 days.[26] Evidence of the validity and accuracy of the WPAI in patients with IBS (WPAI:IBS) has been previously published.[27] The WPAI:IBS was modified for use in patients with IBS-C in phase 3 clinical trials of linaclotide by removing "diarrhea" from the description of symptoms related to IBS to ensure that the questionnaire was specific to the study population.

The WPAI:IBS-C measures 4 domains, including absenteeism (ie, work hours missed because of IBS-C), presenteeism (ie, the degree to which the symptoms of IBS-C affect productivity while at work), overall work productivity loss (ie, absenteeism plus presenteeism resulting from IBS-C), and daily activity impairment (the degree to which the symptoms of IBS-C affect regular daily activities, such as housework, shopping, child care, exercising, studying, etc). Patients with IBS-C who were randomized in the 2 trials completed a self-administered paper version of the WPAI:IBS-C at baseline and at weeks 4, 8, and 12 during the 12-week treatment period for each trial (Trial 1 and Trial 2). In Trial 2, patients also completed the WPAI:IBS-C at weeks 16, 20, and 26. The WPAI:IBS-C scores are represented as percentages, with higher percentages indicating greater work productivity loss and activity impairment.

Patient responses to the following questions on absenteeism, presenteeism, and daily activity impairment were used to calculate the scores for each measure:

- Absenteeism (Q: During the past 7 days, how many hours did you miss from work because of problems associated with your IBS?)
  Calculation = [hours missed/(hours missed + hours worked)] × 100
- Presenteeism (Q: During the past 7 days, how much did IBS symptoms affect your productivity while you were working?)
  Calculation = (item score/10) × 100
- Overall work productivity loss
  Calculation = [absenteeism + (hours worked × presenteeism)] × 100
- Daily activity impairment (Q: During the past 7 days, how much did IBS symptoms affect your ability to do your regular daily activities, other than work at a job?)
  Calculation = (item score/10) × 100.

The WPAI:IBS-C was translated into US Spanish by bilingual translators through a harmonization process of forward and back translations.[28,29]

Statistical Analyses

The analyses of all WPAI:IBS-C measures were based on the intent-to-treat (ITT) population and used the last postbaseline observation carried forward for missing assessments. The analysis cohort included patients with a baseline and at least 1 postbaseline WPAI:IBS-C assessment. The mean WPAI:IBS-C scores for daily activity impairment were computed for all patients. The mean scores for absenteeism, presenteeism, and overall work productivity loss were calculated for employed patients only.

Changes from baseline to weeks 4, 8, and 12 for all 4 WPAI:IBS-C scores for pooled phase 3 clinical trial data were assessed using an analysis of covariance

Table 1 Demographic Characteristics and Mean Baseline WPAI:IBS-C Scores of the Pooled Analysis Cohort

Demographics	Placebo (N = 772)	Linaclotide (N = 783)	Total (N = 1555)
Age			
Mean, yrs	43.9	44.1	44
≥65 yrs, N (%)	43 (5.6)	41 (5.2)	84 (5.4)
Sex			
Female, N (%)	687 (90)	717 (91.6)	1404 (90.3)
Race			
White, N (%)	593 (76.8)	616 (78.7)	1209 (77.8)
Other, N (%)	179 (23.2)	167 (21.3)	346 (22.3)
Baseline WPAI:IBS-C scores, mean			
Absenteeism, % (N)	2.8 (486)	3.1 (512)	3 (998)
Presenteeism, % (N)	33.1 (495)	33.7 (529)	33.4 (1024)
Overall work productivity loss (absenteeism + presenteeism), % (N)	34.5 (486)	35.7 (512)	35.1 (998)
Daily activity impairment, % (N)	39.9 (772)	40.1 (783)	40 (1555)

WPAI:IBS-C indicates Work Productivity and Activity Impairment Questionnaire for Irritable Bowel Syndrome with Constipation.

(ANCOVA) model with the baseline score as a covariate and the treatment group and protocol as factors. In analyses of data from Trial 2, changes from baseline to weeks 4, 8, 12, 16, 20, and 26 for all 4 WPAI:IBS-C scores were assessed using an ANCOVA model with the baseline score as a covariate and the treatment group as a factor. The treatment effects were measured as the least-squared mean difference between linaclotide and placebo based on the ANCOVA results. All treatment comparisons were performed at a nominal $P < .05$ significance level.

Indirect Costs

The calculation of average work hours lost as a result of overall work productivity loss reported among the analysis cohort assumed full-time employment of 40 hours weekly and 2080 hours of potential work time annually per employed patient. The overall work productivity losses were converted into monetary values using the human capital–cost approach,[30] by multiplying the total number of hours lost by the average hourly employment cost of a US employee ($31.16 in September 2013, comprising an average hourly wage of $21.54 and average benefits worth $9.61).[31] All costs are reported in 2013 US dollars, unless otherwise noted.

Results

Demographic and Clinical Characteristics

The pooled ITT population included a total of 1602 patients from the 2 phase 3 clinical trials of linaclotide. The patients' mean age was 44 years, and the majority (90.1%) of patients were female. The pooled analysis cohort included 1555 (97.1%) patients from the 2 trials who completed a baseline and at least 1 postbaseline WPAI:IBS-C assessment (783 patients receiving linaclotide and 772 receiving placebo), of which 1148 (71.7%) patients were currently employed (585 patients receiving linaclotide and 563 receiving placebo). The demographic characteristics of the pooled analysis cohort are shown in **Table 1**.

For analyses conducted over 26 weeks based on data from Trial 2,[25] a total of 804 patients were included in the ITT population. The mean age was 44 years, and the treatment groups were well balanced with respect to demographics, except that the placebo group had a greater proportion of males compared with the linaclotide group (12.7% vs 8.2%, respectively; $P = .038$).[25] The analysis cohort comprised a total of 780 (97%) patients from Trial 2 who completed a baseline WPAI:IBS-C assessment and at least 1 postbaseline WPAI:IBS-C assessment (N = 390 each in the cohorts receiving linaclotide and placebo). Of these, 586 (75.1%) patients were currently employed (294 patients receiving linaclotide and 292 receiving placebo).

Work Productivity and Daily Activity Impairment

At baseline, 20.7% of patients reported missing time from work, 82.4% reported reduced productivity while at work, and 88.7% reported impairment in daily activities as a result of their IBS-C. Based on baseline results of the WPAI:IBS-C, these patients had approximately 3% absenteeism, 33.4% presenteeism, 35.1% overall work productivity loss, and 40% daily activity impairment during the previous 7 days as a result of IBS-C, regardless of treatment assignment (Table 1).

Table 2 shows the changes from baseline in work productivity and daily activity impairment outcomes at weeks 4, 8, and 12 among the pooled analysis cohort by treatment group. Significant reductions in presenteeism, overall work productivity loss, and daily activity impairment were seen for patients receiving linaclotide compared with patients receiving placebo as early as week 4 (all $P < .01$) and remained significant at week 8 (all $P < .01$) and week 12 (all $P < .001$). A numerically greater decrease in absenteeism was also observed in patients receiving linaclotide compared with those receiving placebo from baseline to weeks 4, 8, and 12, but this reduction was not statistically significant.

The treatment effect for linaclotide compared with

Table 2 Mean WPAI Scores for Linaclotide versus Placebo, by Treatment Group (Analysis Cohort)

	Data pooled across Trials 1 and 2						Trial 2 data only					
WPAI:IBS-C outcomes	Week 4, mean % (N[a])	CFB	Week 8, mean % (N[a])	CFB	Week 12, mean % (N[a])	CFB	Week 16, mean % (N[a])	CFB	Week 20, mean % (N[a])	CFB	Week 26, mean % (N[a])	CFB
Absenteeism												
Linaclotide	1.8 (431)	–1.4	2 (455)	–1.1	1.5 (457)	–1.6	1.5 (280)	–2.1	1.2 (283)	–2.4	2.1 (284)	–1.6
Placebo	1.9 (414)	–0.9	1.8 (443)	–1	1.9 (445)	–0.9	2.7 (273)	0.1	2.5 (277)	–0.3	2.4 (279)	–0.7
P value[b]	.761		.864		.311		.056		.023		.718	
Presenteeism												
Linaclotide	17 (459)	–16.7	15.4 (471)	–18.2	15.3 (472)	–18.4	15.7 (283)	–16.8	15.2 (285)	–17.8	15.7 (286)	–17.5
Placebo	20.9 (447)	–12.5	19.3 (458)	–14.2	20.4 (458)	–13.1	20.8 (280)	–12	20.3 (282)	–12.3	21.5 (284)	–11.3
P value[b]	<.001		.002		<.001		.011		.002		<.001	
Overall work productivity loss												
Linaclotide	18.4 (431)	–17.2	16.8 (455)	–18.6	16 (457)	–19.4	16.3 (280)	–18.5	15.7 (283)	–19.7	16.4 (284)	–19.2
Placebo	22.3 (414)	–12.4	20.3 (443)	–14.7	21.9 (445)	–13	23.4 (273)	–10.8	22.3 (277)	–11.9	22.6 (279)	–11.2
P value[b]	.002		.007		<.001		<.001		<.001		<.001	
Daily activity impairment												
Linaclotide	21.9 (783)	–18.2	20.4 (783)	–19.7	20.2 (783)	–19.9	20.6 (390)	–18.8	19.8 (390)	–19.7	20.2 (390)	–19.3
Placebo	25.2 (771)	–14.7	24.1 (772)	–15.8	24.8 (772)	–15.2	25.7 (390)	–14.2	24.4 (390)	–15.6	27.1 (390)	–12.9
P value[b]	.001		<.001		<.001		.001		.004		<.001	

[a]Sample sizes vary as a result of missing information for patients who did not complete all WPAI:IBS-C assessments at all study weeks.
[b]*P* value for weeks 4, 8, and 12 from ANCOVA for least squares mean change from baseline to each week indicated for linaclotide compared with placebo, with baseline score as a covariate and treatment and protocol as factors. *P* value for weeks 16, 20, and 26 from ANCOVA for least squares mean change from baseline to each week indicated for linaclotide compared with placebo, with baseline score as a covariate and treatment as a factor.

NOTES: Absenteeism, presenteeism, and overall work productivity loss (absenteeism + presenteeism) include employed patients only (N = 1148 for pooled cohort; N = 586 for Trial 2). Daily activity impairment includes all patients (N = 1555 for pooled cohort; N = 780 for Trial 2). All scores are presented as percent of impairment.

ANCOVA indicates analysis of covariance; CFB, change from baseline; WPAI:IBS-C, Work Productivity and Activity Impairment Questionnaire for Irritable Bowel Syndrome with Constipation.

placebo is shown in **Table 3**. From baseline to week 12, compared with placebo, treatment with linaclotide was associated with significant reductions of 5.2% for presenteeism, 6.1% for overall work productivity loss, and 4.7% for daily activity impairment (all *P* <.01).

The impact of linaclotide treatment over 26 weeks is provided in Table 2. Treatment with linaclotide was associated with significant reductions from baseline in presenteeism, overall work productivity loss, and daily activity impairment compared with placebo at weeks 4, 8, 12, 16, 20, and 26. Significant reductions observed at weeks 4, 8, and 12 were consistent with analyses of the pooled analysis cohort (data not shown). Absenteeism was reduced at all weeks measured, with increasing reductions seen from weeks 4 through 20, but statistical significance was not achieved (Table 2).

From baseline to week 26, treatment with linaclotide led to significant reductions of 5.9% for presenteeism (*P* <.05), 7.5% for overall work productivity loss (*P* <.001), and 6.7% for daily activity impairment (*P* <.001; Table 3).

These results translate into a reduction in overall work productivity loss (absenteeism plus presenteeism) in the pooled analysis cohort of 2.4 hours weekly at week 12 as a result of treatment with linaclotide, which translates into 127 hours annually. In the 26-week trial, treatment with linaclotide reduced overall work productivity loss by 3 hours weekly at week 26, which translates into 156 hours annually. Based on a potential inflation rate of 33.7% for work productivity loss in patients with IBS caused by errors in 1-week recall, as observed in previous research,[27] a conservative estimate of the difference in work productivity loss between the group receiving pla-

Table 3 Treatment Effect[a] for Linaclotide versus Placebo (Analysis Cohort)

	Data pooled across Trials 1 and 2			Trial 2 data only		
WPAI:IBS-C outcomes	Week 4, %	Week 8, %	Week 12, %	Week 16, %	Week 20, %	Week 26, %
Absenteeism	–0.18	0.10	–0.46	–1.56	–1.42	–0.27
Presenteeism	–4.07[b]	–3.94[b]	–5.21[b]	–4.56[c]	–5.26[c]	–5.92[c]
Overall work productivity loss	–4.27[b]	–3.66[b]	–6.09[b]	–7.28[c]	–7.39[c]	–7.54[c]
Daily activity impairment	–3.40[b]	–3.84[b]	–4.68[b]	–4.87[c]	–4.42[c]	–6.69[c]

[a]Treatment effect = least squares means difference between linaclotide and placebo based on ANCOVA analysis.
[b]P <.01 based on ANCOVA, with baseline score as covariate and treatment group and protocol as fixed effects.
[c]P <.05 based on ANCOVA, with baseline score as covariate and treatment group as a fixed effect.
NOTE: Overall work productivity loss = absenteeism plus presenteeism.
ANCOVA indicates analysis of covariance; WPAI:IBS-C, Work Productivity and Activity Impairment Questionnaire for Irritable Bowel Syndrome with Constipation.

cebo and the group receiving linaclotide is 1.6 hours to 2.4 hours weekly, or 84 hours to 127 hours annually at week 12. Conservative estimates for the 26-week analyses range from 2 hours to 3 hours weekly, or 103 hours to 156 hours annually at week 26.

Indirect Costs

The overall work productivity loss of 35.1% observed among the pooled analysis cohort at baseline translates into an average loss of 14 hours weekly or 730 hours annually before the initiation of treatment. These losses equate to lost costs of $436 weekly or $22,747 annually for each employed patient with IBS-C. Based on the reduction in overall work productivity loss of 103 hours to 156 hours annually that was estimated as a result of treatment with linaclotide in the 26-week analysis, overall work losses of $62 to $93 per patient weekly (or $3209 to $4861 per patient annually) could potentially be avoided.

Discussion

Data from previous studies indicate that the majority of patients seeking healthcare for IBS experience significant impairment in work productivity and daily activities of living. To our knowledge, this study is the first to evaluate the impact of treatment with linaclotide on work productivity and activity impairment and report indirect costs associated with work productivity loss among patients with IBS-C. Previous analyses of work productivity among patients with IBS-C have reported on shorter time frames of 2 weeks and 4 weeks.[32] However, for a chronic condition, such as IBS-C, it is important to be able to assess the long-term impact of this condition and its treatment on patient HRQOL and work productivity. This present study is the first to assess work productivity and daily activity impairment over a longer time period of 12 weeks and 26 weeks.

The baseline WPAI:IBS-C scores reported in our study are comparable with baseline WPAI:IBS-C scores reported in previous research,[32] suggesting that work productivity and daily activity continue to be substantially affected by IBS-C, and there remains a significant unmet need for effective treatments for this condition. The impact of IBS-C on work and daily activity can be put into perspective by comparing it with the impact of other chronic gastrointestinal and nongastrointestinal conditions.

Specifically, baseline presenteeism, overall work productivity loss, and daily activity impairment seen among patients with IBS-C are comparable with impairment observed among patients with severe asthma, moderate-to-severe ulcerative colitis, and Crohn's disease, and higher than the impairment seen among patients with mild-to-moderate gastroesophageal reflux disease (GERD) and mild ulcerative colitis based on the WPAI scores reported for these conditions.[33-36] Furthermore, the indirect costs found among patients with IBS-C in our study are comparable with the indirect costs estimated for patients with GERD[37,38]; however, these comparisons should be made with caution, because methodologies used to estimate the indirect costs differ across studies, and other studies do not always include both absenteeism and presenteeism when calculating indirect costs.

Treatment with linaclotide led to significant reductions in presenteeism, overall work productivity loss, and daily activity impairment compared with placebo. These reductions were observed as early as week 4 and were maintained at all time points, including through week 26 of treatment in a subset of patients. Although no signifi-

cant differences were observed for absenteeism between linaclotide and placebo, a numerically greater decrease in absenteeism was seen for linaclotide compared with placebo. However, baseline absenteeism levels were low for both linaclotide and placebo, which was consistent with previous findings,[19] and the overall work productivity loss was primarily driven by presenteeism, also consistent with previous research.[11,19,20]

Before treatment with linaclotide, the overall work productivity loss resulting from IBS-C corresponded to an average of 730 work hours lost annually, equating to annual indirect costs of $22,747 per patient for employed patients in this study. The reduction in overall work productivity loss estimated as a result of treatment with linaclotide at week 26 of 103 hours to 156 hours annually could result in an avoided overall work loss of $62 to $93 per patient weekly, or $3209 to $4861 per patient annually.

Limitations

Although the 7-day patient recall period used in the WPAI is considered acceptable for health economic evaluations and has been tested in all previous WPAI validation studies, including the IBS-specific version,[27] a shorter recall period may improve the accuracy of patient responses. In addition, although the long-term impacts of treatment with linaclotide on work productivity and daily activity impairment were assessed based on 26 weeks of treatment, this could only be evaluated based on the data from 1 trial.

Estimates of the indirect costs associated with IBS-C and treatment with linaclotide were extrapolated based on average 2013 US wage data and may not be representative of all employed patients with IBS-C.

Furthermore, this analysis was conducted among patients meeting modified Rome II criteria for IBS-C and may not be sufficiently representative of all patients with IBS-C in the general population.

Conclusion

IBS-C continues to represent a significant burden for patients and employers. Once-daily treatment with linaclotide was associated with significant reductions in overall work productivity loss and daily activity impairment compared with placebo among patients with IBS-C, with significant benefits observed at all time points measured through 26 weeks of treatment. Assuming a 40-hour work week, treatment with linaclotide reduced overall work productivity loss by 2.4 hours weekly at week 12 and by 3 hours weekly by week 26.

Adding to the current body of literature on the economic burden of IBS-C in the United States, this is the first study to provide estimates of the indirect costs to employers associated with this condition. From an employer's perspective, therapies for IBS-C that effectively manage this chronic, symptomatic condition and improve employee HRQOL and work productivity may represent significant cost-savings in the form of avoided work productivity losses that are associated with IBS-C. ■

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Author Disclosure Statement

Ms Buono owns stock/stock options in Actavis plc; Dr Tourkodimitris owns stock/stock options in Actavis plc; Mr Sarocco owns stock in Ironwood Pharmaceuticals, Inc; Dr Johnston has stock option holdings in Ironwood Pharmaceuticals, Inc; Ms Carson owns stock/stock options in Actavis plc.

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STAKEHOLDER PERSPECTIVE

Patient-Reported Outcomes Matter

By Walid F. Gellad, MD, MPH
Staff Physician, VA Pittsburgh Healthcare System, Codirector, University of Pittsburgh Center for Pharmaceutical Policy and Prescribing, PA

Abdominal pain is the leading gastrointestinal (GI) symptom prompting a visit to an outpatient clinic, with almost 16 million visits nationally in 2009.[1] Diarrhea and constipation are the second and third leading symptoms, respectively.[1] Regardless of whether they result from diagnosed functional disorders such as irritable bowel syndrome (IBS), these GI symptoms lead to substantial reductions in quality of life and work productivity. The article by Buono and colleagues focuses on IBS with constipation (IBS-C) and examines a key patient-reported outcome: work productivity and activity impairment.[2] Their study highlights the importance of understanding patient-reported outcomes that matter not only to patients, but also to employers.[3]

PATIENTS/PROVIDERS: There is great interest in the use of patient-reported outcomes in clinical research and performance improvement.[4-6] Studies of linaclotide in patients with IBS-C exemplify the use of these patient-reported outcomes to measure key symptoms that matter to patients, including abdominal pain, number of spontaneous bowel movements, and work productivity and activity impairment.[7,8] Patients can more easily understand, and providers can more easily explain, the benefits of particular medications for symptom management when relevant symptoms are included as outcomes. Employers also can more easily translate the potential benefits of a therapy to their bottom line, as Buono and colleagues demonstrate. It is much more difficult to articulate a clear interpretation of benefits for employers in studies using more "objective," but perhaps more "inaccessible," outcomes; consider, as an example, the endoscopic resolution of erosive esophagitis in clinical trials of proton pump inhibitors.[9]

Although the use of the Work Productivity and Activity Impairment Questionnaire for IBS-C is well validated in patients with IBS,[10] in studies involving linaclotide, the questionnaire was minimally modified to remove "diarrhea" from the description of an IBS-related symptom, according to Buono and colleagues. Guidance from the US Food and Drug Administration on the use of patient-reported outcomes to support labeling indications emphasizes the importance of avoiding instrument

STAKEHOLDER PERSPECTIVE *Continued*

modification.[11] The particular modification in the linaclotide studies is relevant, given that diarrhea is the most common side effect of linaclotide. Any improvement for patients in work productivity resulting from improvements in abdominal pain and constipation must be balanced against any potential loss related to the medication's side effects, such as diarrhea.

EMPLOYERS/PAYERS: Taken together, the findings of studies of linaclotide demonstrate improvements in many important patient-reported domains when compared with placebo, including work productivity. However, employers need additional information to truly understand the potential benefit of providing insurance coverage for such a therapy for their employees, namely, the effectiveness of such drugs compared with older, less-expensive therapies rather than comparing them only with placebo. Employers, and payers, want to know how to maximize the benefits while minimizing treatment costs.

Other treatments, such as dietary modifications, increased physical activity, polyethylene glycol, and fiber, all have a role in the treatment of IBS-C, and linaclotide must be evaluated in the context of such therapies as well. Furthermore, only a small proportion of patients with IBS-C who receive linaclotide respond to the treatment[12]; therefore, there is a need to identify who is most likely to respond and who is unlikely to respond.

These questions do not take away from the importance of the study findings by Buono and colleagues, but they are emblematic of the difficulty in truly translating clinical trial findings into clinical reality. ■

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