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ORIGINAL RESEARCH

Treatment-Free Interval: A Novel Approach to Assessing Real-World Treatment Effectiveness and Economic Impact Among Patients with Irritable Bowel Syndrome with Diarrhea

Brian E. Lacy · Patrick Gagnon-Sanschagrin · Zeev Heimanson · Rebecca Bungay · Remi Bellefleur · Annie Guérin · Brock Bumpass · Danellys Borroto · George Joseph · Ankur A. Dashputre

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ABSTRACT

Introduction: Objective assessment of treatment effectiveness using real-world claims data is challenging. This study assessed treatment-free intervals (TFI) as a proxy for treatment effectiveness, and all-cause healthcare costs among adult patients with irritable bowel syndrome with diarrhea (IBS-D) treated with rifaximin or eluxadoline in the USA.

Methods: Adult patients (18–64 years) with IBS-D and ≥ 1 rifaximin or eluxadoline prescription were identified in the IQVIA PharMetrics® Plus database (10/01/2015–12/31/2021) and classified into two mutually exclusive cohorts (i.e., rifaximin and eluxadoline). Index date was the date of rifaximin or eluxadoline initiation. Entropy-balanced baseline characteristics, TFI (periods of ≥ 30 consecutive days without IBS-D treatment), and healthcare costs were reported. Healthcare costs were compared between cohorts using mean cost differences.

Results: There were 7094 and 2161 patients in the rifaximin and eluxadoline cohorts, respectively. After balancing, baseline characteristics (mean age 44.1 years; female 72.4%) were similar between cohorts. A higher proportion of patients treated with rifaximin achieved a TFI of ≥ 30 days (76.2% vs. 66.7%), ≥ 60 days (67.0% vs. 47.0%), ≥ 90 days (61.0% vs. 38.7%), ≥ 180 days (51.7% vs. 31.0%), and ≥ 240 days (47.7% vs. 27.9%) compared to eluxadoline. Among patients with a TFI ≥ 30 days, mean TFI durations were 8.3 and 6.0 months for the rifaximin and eluxadoline cohorts. Mean all-cause healthcare costs were lower for rifaximin vs. eluxadoline ($18,316 vs. $23,437; $p = 0.008$),

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B. E. Lacy
Division of Gastroenterology, Mayo Clinic, Jacksonville, FL, USA

P. Gagnon-Sanschagrin · R. Bungay (✉) · R. Bellefleur · A. Guérin
Analysis Group, Inc., 1190 Avenue Des Canadiens-de-Montréal, Suite 1500, Montréal, QC H3B 0G7, Canada
e-mail: Rebecca.Bungay@analysisgroup.com

Z. Heimanson
Salix Pharmaceuticals, Bridgewater Township, NJ, USA

B. Bumpass · D. Borroto · G. Joseph · A. A. Dashputre
Bausch Health, Bridgewater Township, NJ, USA

G. Joseph
BioNTech US Inc., 40 Erie St, Cambridge, MA 02139, USA

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primarily driven by pharmacy costs ($7348 vs. $10,250; $p < 0.001$). In a simulated health plan of one million commercially insured lives, initiating 50% of patients on rifaximin instead of eluxadoline resulted in total cost savings of $2.1 million per year or $0.18 per-member-per-month.

Conclusions: This real-world study suggests that TFI is a meaningful surrogate measure of treatment effectiveness in IBS-D. Patients treated with rifaximin had longer treatment-free periods and lower healthcare costs than patients treated with eluxadoline.

Keywords: Eluxadoline; Irritable bowel syndrome; Real-world; Rifaximin; Treatment-free interval

Key Summary Points

Why carry out this study?

Real-world data comparing treatments for irritable bowel syndrome with diarrhea (IBS-D) are limited, and it is difficult to assess real-world treatment effectiveness and associated outcomes, such as healthcare costs, using health administrative claims data.

The objective of the present study was to describe and compare treatment-free intervals (TFIs) and healthcare costs among adults with IBS-D treated with rifaximin or eluxadoline using claims data for a commercially insured population in the USA.

What was learned from the study?

Patients with IBS-D who initiated treatment with rifaximin required shorter treatment durations, remained treatment-free longer, and had lower all-cause healthcare costs than those who initiated eluxadoline.

The TFI may be a valuable proxy for measuring effectiveness of prescription medication in patients with IBS-D, and provides a novel way of assessing treatment effectiveness using real-world claims data.

Patients with IBS-D may benefit from treatment with rifaximin compared to eluxadoline, as rifaximin may allow patients to remain treatment-free for longer periods and is associated with lower healthcare costs.

INTRODUCTION

Irritable bowel syndrome (IBS) with diarrhea (IBS-D) is a common, chronic, relapsing, and potentially severe disorder of gut–brain interaction (DGBI) characterized by troublesome symptoms such as abdominal pain, diarrhea, fecal urgency, and bloating [1–4]. IBS affects 7.4% of adults in the USA, among whom 29.6% are diagnosed with IBS-D [5].

Clinical management of IBS-D is complicated by the heterogenous presentation of the condition and multiple treatments are often needed to manage symptoms [1, 3, 6]. Historically, antispasmodics and over-the-counter medications, such as antidiarrheals, have been used [3]; however, these treatments do not typically improve abdominal pain or bloating. In recent years, the US Food and Drug Administration (FDA) has approved three agents for the treatment of IBS-D: rifaximin (an antibiotic), eluxadoline (a mixed opioid receptor agonist/antagonist), and alosetron (a serotonin antagonist) [7–10]. Among these approved treatments, rifaximin and eluxadoline are indicated for adults with IBS-D [8, 9], while alosetron is indicated only for women with severe IBS-D [10]. Both rifaximin and eluxadoline can reduce global IBS symptoms, as well as improve stool consistency and visceral pain [8, 9, 11, 12]. Although these agents are among the most commonly used prescription medications in patients with IBS-D [4, 7] and both have shown significant improvement in clinical outcomes

assessed in their respective clinical trials [11–13], no head-to-head studies or comprehensive comparisons of their clinical and economic outcomes in a real-world setting have been conducted.

Real-world data allow for the assessment of treatment effectiveness among complex and diverse patient populations encountered in routine clinical practice, outside of the controlled environments of clinical trials [14, 15]. However, assessing real-world treatment effectiveness among patients with IBS-D may be challenging because of differences in symptom presentation [16, 17]. Specifically, the degree of treatment response (e.g., relief of some symptoms and not others), duration of treatment response (including fluctuation in symptom relief), and lack of a standard measure for treatment response in IBS-D may complicate the assessment.

The FDA recommends using multi-item patient-reported outcomes that capture clinically important signs and symptoms to define treatment effects in clinical trials [18]. For example, the IBS-severity scoring system is a validated five-item patient-reported gastrointestinal symptom (GI) questionnaire that measures the frequency and intensity of abdominal pain, severity of abdominal distension, dissatisfaction with bowel habits, and the interference of IBS with daily life [19]. However, such assessments are challenging to use outside of a clinical trial setting, and it is difficult to evaluate real-world clinical outcomes of IBS-D treatments, as well as possible associations with other outcomes, such as healthcare costs. A treatment-free interval (TFI), which refers to the length of time a patient remains off treatment after a course of therapy, may represent a novel approach to evaluate IBS-D treatment effectiveness in a real-world setting. Although not previously studied in any DGBI condition, the TFI may serve as a valuable proxy to evaluate the effectiveness of treatments for diseases such as IBS-D in studies using health administrative claims databases [17], which are widely used as patient data sources in real-world analyses [20]. The TFI may also allow for comparisons across multiple prescription medications.

The present study aimed to describe and compare the TFIs and all-cause healthcare costs among adult patients with IBS-D treated with rifaximin or eluxadoline using US commercial claims data.

METHODS

Data Source

Analyses were performed using data extracted from the IQVIA PharMetrics® Plus database (October 1, 2015–December 31, 2021) [21]. PharMetrics® Plus contains comprehensive, integrated claims data of over 210 million unique beneficiaries since 2006, of which over 170 million are covered by both medical and pharmacy plans. Data contributors to the database are largely commercial health plans. It is representative of the commercially insured US national population for patients under 65 years of age. It contains a longitudinal view of inpatient and outpatient services, prescription and office/outpatient administered drugs, costs, and detailed enrollment information. Data are de-identified and comply with the requirements of the Health Insurance Portability and Accountability Act; therefore, no institutional review board exemption nor informed consent was required for this study.

Study Design

This was a retrospective study conducted on commercially insured adult patients with IBS-D who received at least one prescription of rifaximin (550 mg thrice daily) or eluxadoline (100 mg twice daily), regardless of pre-treatment with other IBS-D agents (i.e., antiperistaltics, antispasmodics, mixed opioid agonists/antagonists, and tricyclic agents; Fig. 1) [4]. The index date was defined as the date when the index agent, rifaximin or eluxadoline, was initiated. The index treatment began on the index date, encompassing multiple fills of the index agent, as well as any other IBS-D treatment (excluding rifaximin or eluxadoline) if the other agent was initiated within the days of supply of

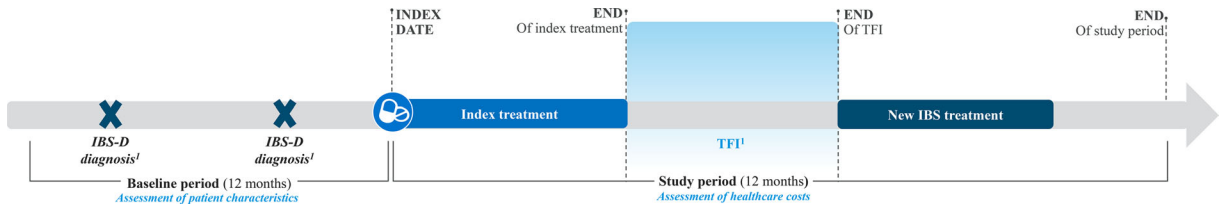

Fig. 1 Study design. [1]Patients were required to have ≥ 2 IBS-D diagnoses, with ≥ 1 diagnosis during the baseline period. The second IBS-D diagnosis could occur at any time during the patient's continuous health plan enrollment. [2]The TFI is for illustrative purposes; all potential scenarios are not demonstrated. *IBS-D* irritable bowel syndrome with diarrhea, *TFI* treatment-free interval

the initial fill of the index agent. The index treatment ended at the first occurrence of 30 days or more without any prescription fills of the index agent, a prescription fill for a new IBS-D agent (i.e., other than those included in the index treatment), or the end of data availability.

The baseline period was defined as the 12 months prior to the index date. The study period was defined as the 12 months following the index date.

Sample Selection

Patients were included in the study if they met the following criteria: (1) ≥ 2 IBS-D diagnoses (International Classification of Disease, Tenth Revision, Clinical Modification [ICD-10-CM] K58.0) on distinct dates; (2) no indicator of hepatic encephalopathy [22] or traveler's diarrhea (defined as a diagnosis of infectious gastroenteritis [ICD-10-CM A09] or a prescription fill for rifaximin 200 mg); (3) ≥ 1 prescription fill for rifaximin or eluxadoline; (4) ≥ 12 months of continuous health plan enrollment before and after the index date; (5) aged 18–64 years as of the index date (Fig. 2). Patients were excluded from the study if they had claims for simultaneous use of rifaximin and eluxadoline.

Study Cohorts and Balancing

All eligible patients were classified into two mutually exclusive cohorts based on the index agent: rifaximin cohort and eluxadoline cohort. Entropy balancing was used to balance key characteristics that may have had an impact on the differences in outcomes across cohorts [23]. Briefly, entropy balancing reweights observations between groups to ensure comparable populations, where weights are assigned to patients in one cohort such that the specified covariate distribution will have the same mean and standard deviation as the other cohort. In this study, patient characteristics from the eluxadoline cohort were weighted to match those in the rifaximin cohort, with the characteristics in the rifaximin cohort remaining the same before and after balancing. Absolute standardized differences (aSD) were reported before and after balancing.

Characteristics used for balancing included those selected a priori on the basis of medical expert input and variables with an aSD ≥ 0.2. These included age, sex, calendar year of index date, healthcare plan type, region, provider type, number of IBS agents during baseline, GI-related and mental health-related diagnoses, baseline procedures, and baseline treatments.

Characteristics and Study Outcomes

Patient characteristics included age, sex, health plan type, region, and provider specialty, as of the index date. During baseline, medically relevant comorbidities (both GI-related and mental health-related), procedures (i.e., anesthesia, surgery, radiation services and therapies), and treatments were reported.

During the 1-year study period, characteristics of the index treatment were assessed. Specifically, the duration of the index treatment and the number of fills were reported.

Study outcomes included TFIs and all-cause healthcare costs. A TFI was defined as a period

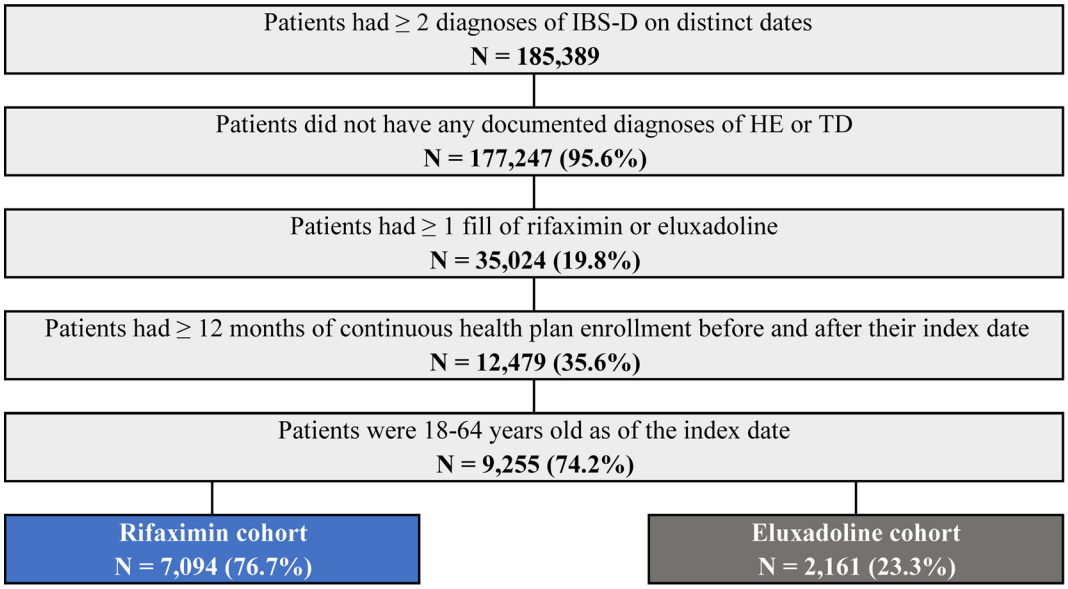

Fig. 2 Sample selection criteria. *HE* hepatic encephalopathy, *IBS-D* irritable bowel syndrome with diarrhea, *TD* traveler's diarrhea

of at least 30 consecutive days without any IBS-D treatments observed. In this study, TFI specifically referred to relapses requiring medical attention, and did not include over-the-counter medications or mild symptoms not requiring prescription medications. During the study period, the proportion of patients who achieved a TFI, the duration of the TFI (i.e., ≥ 30 days, ≥ 60 days, ≥ 90 days, ≥ 180 days, ≥ 240 days), and the proportion of patients who remained treatment-free at the end of the study period were reported. All-cause healthcare costs were reported per patient per year (PPPY) and included medical costs (inpatient, outpatient, and emergency department) and pharmacy costs. Costs were measured during the 1-year study period, adjusted for inflation using the US Medical Care consumer price index [24], and reported from the payer's perspective in 2021 US dollars, reflecting the total amount reimbursed by the payer and the coordination of benefits, excluding deductibles and patient copayments. To assess the impact of initiating treatment with rifaximin instead of eluxadoline, healthcare cost savings (annual and per member per month [PMPM]) of patients with IBS-D were estimated among a simulated healthcare plan of one million commercially insured lives.

Statistical Analyses

For all outcomes, continuous variables were summarized using means, standard deviations, and medians, while categorical variables were summarized using frequency counts and percentages. All measures and outcomes were reported among each cohort separately.

Healthcare costs during the 1-year study period were compared between the rifaximin and eluxadoline cohorts using weighted generalized linear regression models with a Gamma distribution and a log link, using robust standard errors. Mean differences (MD) for the entropy-balanced cohort were reported with 95% confidence intervals (CIs) and *p* values, with significance considered at the 5% level.

RESULTS

Patient Characteristics

A total of 9255 patients met the sample selection criteria; 7094 and 2161 patients were

Table 1 Patient characteristics

	Rifaximin cohort (N = 7094)	Before balancing		After balancing	
		Eluxadoline cohort (N = 2161)	aSD	Eluxadoline cohort (N = 2161)	aSD
As of the index date					
Age					
Mean ± SD, years	44.1 ± 12.8	43.2 ± 13.1	0.07	44.1 ± 12.8	0.00
Median (Q1–Q3), years	45.0 (34.0–55.0)	44.0 (32.0–55.0)	–	46.0 (34.0–55.0)	–
18–24 years old, N (%)	692 (9.8%)	248 (11.5%)	0.06	211 (9.8%)	0.00
25–34 years old, N (%)	1121 (15.8%)	379 (17.5%)	0.05	342 (15.8%)	0.00
35–44 years old, N (%)	1595 (22.5%)	471 (21.8%)	0.02	486 (22.5%)	0.00
45–54 years old, N (%)	1744 (24.6%)	515 (23.8%)	0.02	531 (24.6%)	0.00
55–64 years old, N (%)	1942 (27.4%)	548 (25.4%)	0.05	592 (27.4%)	0.00
Female, N (%)	5133 (72.4%)	1379 (63.8%)	0.18	1564 (72.4%)	0.00
Calendar year of index date, N (%)					
2016	391 (5.5%)	244 (11.3%)	0.21	119 (5.5%)	0.00
2017	1414 (19.9%)	672 (31.1%)	0.26	431 (20.0%)	0.00
2018	1749 (24.7%)	561 (26.0%)	0.03	533 (24.7%)	0.00
2019	1936 (27.3%)	395 (18.3%)	0.22	590 (27.3%)	0.00
2020	1596 (22.5%)	286 (13.2%)	0.24	486 (22.5%)	0.00
2021	8 (0.1%)	3 (0.1%)	0.01	2 (0.1%)	0.01
Region, N (%)					
South	3401 (47.9%)	1167 (54.0%)	0.12	1037 (48.0%)	0.00
Northeast	1508 (21.3%)	324 (15.0%)	0.16	459 (21.2%)	0.00
Midwest	1313 (18.5%)	509 (23.6%)	0.12	403 (18.6%)	0.00
West	863 (12.2%)	161 (7.5%)	0.16	263 (12.2%)	0.00
Unknown/missing	9 (0.1%)	0 (0.0%)	0.05	0 (0.0%)	0.05
During the baseline period					
Healthcare plan type, N (%)					
PPO	5515 (77.7%)	1750 (81.0%)	0.08	1668 (77.2%)	0.01
HMO	830 (11.7%)	214 (9.9%)	0.06	253 (11.7%)	0.00
POS	549 (7.7%)	144 (6.7%)	0.04	182 (8.4%)	0.03
CDHP	157 (2.2%)	37 (1.7%)	0.04	39 (1.8%)	0.03
Other	43 (0.6%)	16 (0.7%)	0.02	19 (0.9%)	0.03

Table 1 continued

	Rifaximin cohort (*N* = 7094)	Before balancing		After balancing	
		Eluxadoline cohort (*N* = 2161)	aSD	Eluxadoline cohort (*N* = 2161)	aSD
Provider specialty, *N* (%)					
Gastroenterologist	3857 (54.4%)	585 (27.1%)	0.58	1174 (54.3%)	0.00
Other specialty	2839 (40.0%)	1254 (58.0%)	0.37	866 (40.1%)	0.00
Family practice	1037 (36.5%)	623 (28.8%)	0.35	317 (14.7%)	0.00
Internal medicine	603 (21.2%)	254 (11.8%)	0.11	184 (8.5%)	0.00
Unknown/missing	398 (5.6%)	322 (14.9%)	0.31	121 (5.6%)	0.00
Number of IBS-D agents in baseline[a]					
Mean ± SD	0.8 ± 1.1	1.0 ± 1.2	0.12	0.8 ± 1.1	0.00
Median (Q1–Q3)	0.0 (0.0–1.0)	1.0 (0.0–2.0)	–	0.0 (0.0–1.0)	–
Number of IBS-D treatment fills in baseline[a]					
Mean ± SD	1.8 ± 3.4	2.3 ± 3.9	0.13	1.9 ± 3.5	0.01
Median (Q1–Q3)	0.0 (0.0–2.0)	1.0 (0.0–3.0)	–	0.0 (0.0–2.0)	–
During the study period					
Index treatment characteristics					
Mean ± SD					
Duration of index treatment (months)	0.6 ± 0.4	3.5 ± 3.7	–	–	–
Number of treatment fills	1.2 ± 0.6	2.9 ± 3.2	–	–	–
Median (Q1–Q3)					
Duration of index treatment (months)	0.5 (0.5–0.5)	1.3 (1.0–4.4)	–	–	–
Number of treatment fills	1.0 (1.0–1.0)	1.0 (1.0–3.0)	–	–	–

ACG American College of Gastroenterology, *aSD* absolute standardized difference, *CDHP* consumer driven health plan, *HMO* home maintenance organization, *IBS* irritable bowel syndrome, *IBS-D* irritable bowel syndrome with diarrhea, *N* number, *POS* point of service, *PPO* preferred provider organization, *SD* standard deviation

[a]IBS-D treatments were defined according to 2021 ACG guidelines: antiperistaltics, antispasmodics, bile acid sequestrants, tricyclic agents, and IBS agents. IBS agents are defined as rifaximin, eluxadoline, and alosetron

included in the rifaximin and eluxadoline cohorts, respectively (Fig. 2).

After balancing, baseline characteristics between the rifaximin and eluxadoline cohorts were similar (Table 1). Mean patient age was 44.1 years, and 72.4% of patients were female. During the baseline period, patients received an average of 0.8 IBS-D agents, with 1.8 and 1.9 fills for the rifaximin and eluxadoline cohorts, respectively. Baseline medications included glucocorticosteroids (30.2% and 34.0% in the rifaximin and eluxadoline cohorts,

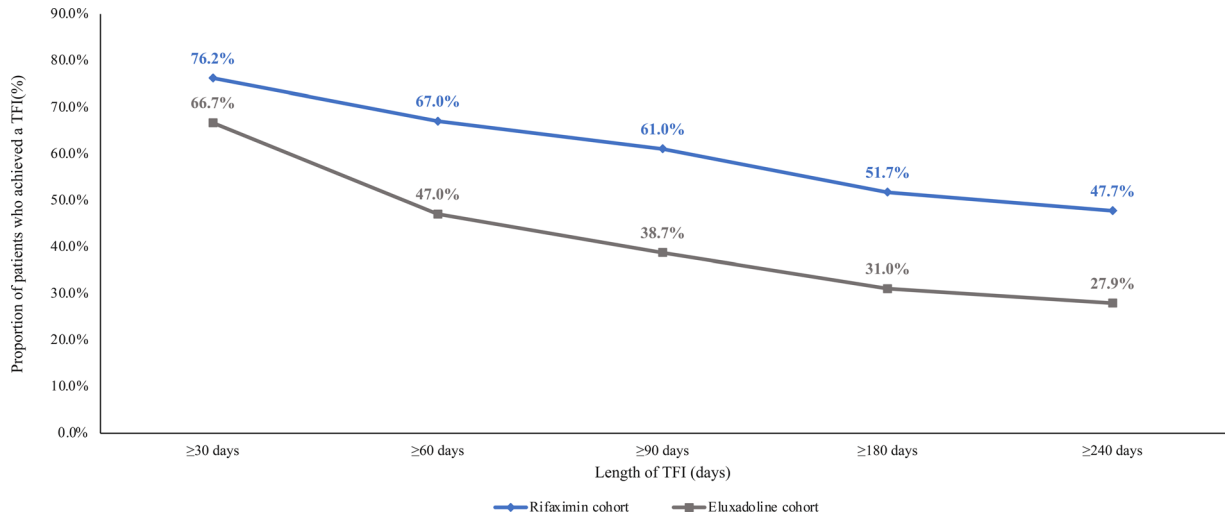

Fig. 3 Proportion of patients who achieved a TFI. *SD* standard deviation, *TFI* treatment-free interval

respectively), azithromycin (19.6% and 19.6%), and laxatives (18.0% and 18.0%) (Supplementary Material). For the index treatment, mean treatment duration was 0.6 and 3.5 months with an average of 1.2 and 2.9 fills in the rifaximin and eluxadoline cohorts, respectively. Information on baseline treatments, diagnoses, and procedures are summarized in Supplementary Material.

Treatment-Free Interval

After balancing, more patients treated with rifaximin achieved a TFI across all time points compared to patients who received eluxadoline; specifically, $\geq$ 30 days (76.2% vs. 66.7%), $\geq$ 60 days (67.0% vs. 47.0%), $\geq$ 90 days (61.0% vs. 38.7%), $\geq$ 180 days (51.7% vs. 31.0%), and $\geq$ 240 days (47.7% vs. 27.9%). Among patients who achieved a TFI, mean TFI duration was 8.3 months in the rifaximin cohort and 6.0 months in the eluxadoline cohort, with 56.6% and 42.7% of patients, respectively, still on a TFI at the end of the study period (Fig. 3).

Healthcare Costs

Total all-cause healthcare costs during the 1-year study period were significantly lower for the rifaximin cohort compared to the eluxadoline cohort ($18,316 vs. $23,437 PPPY; MD –$5120, $p = 0.008$). The difference in healthcare costs was mainly driven by lower pharmacy costs in the rifaximin cohort ($7348 vs. $10,250 PPPY; MD –$2902, $p < 0.001$). Although medical costs were numerically lower in the rifaximin cohort compared with the eluxadoline cohort ($10,969 vs. $13,186 PPPY), the differences were not significant (Fig. 4).

In a simulated health plan of one million commercially insured lives, if payers and physicians ensured that 50% of eluxadoline-treated patients with IBS-D were initiated on rifaximin instead of eluxadoline, the total cost savings would amount to $2.1 million per year, or approximately $0.18 PMPM (Fig. 5).

DISCUSSION

In this real-world retrospective cohort study, patients with IBS-D who initiated treatment with rifaximin required shorter treatment durations, remained treatment-free longer after initiating rifaximin, and had lower all-cause healthcare costs compared with those who initiated eluxadoline.

Given the challenges inherent to using claims data to directly assess effectiveness of IBS-D treatments [16, 17], this study analyzed TFIs to compare two IBS-D prescription

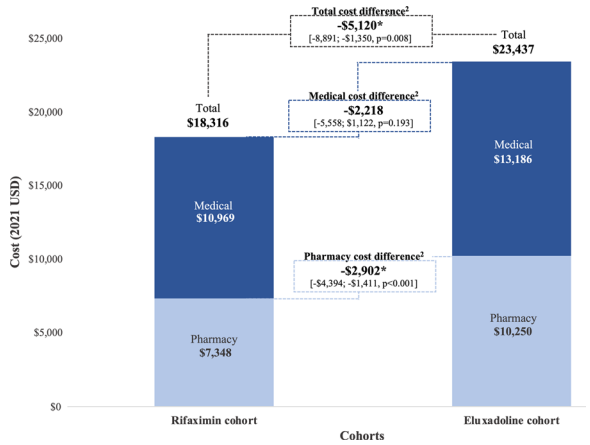

Fig. 4 Comparison of all-cause healthcare costs[1] differences between rifaximin and eluxadoline cohort. *$p < 0.05$. [1]Healthcare costs were measured from the payer's perspective during the 1-year study period and reported as average annual costs per patient per year in 2021 USD. [2]Weighted cost differences, 95% confidence intervals, and p values were obtained using a weighted generalized linear model with a Gamma distribution, a log link function, and robust standard errors. [3]Healthcare costs summary statistics (SD, median, Q1–Q3) by cohort: Rifaximin cohort—Total costs SD = $38,006, median = $8206, Q1–Q3 $4148–$17,549; Medical costs SD = $24,956, median = $3756, Q1–Q3 $1323–$9692; Pharmacy costs SD = $25,509, median = $3082, Q1–Q3 $1777–$6006; Eluxadoline cohort—Total costs SD = $37,643, median = $12,136, Q1–Q3 $5932–$22,649; Medical costs SD = $33,078, median = $3302, Q1–Q3 $1247–$10,048; Pharmacy costs SD = $15,011, median = $6109, Q1–Q3 $2401–$12,043. *SD* standard deviation, *USD* US dollar

medications, rifaximin and eluxadoline. Current evidence from studies evaluating TFIs in oncology treatments indicate that the TFI can be a valuable measure of real-world treatment success, where patients with cancer value treatment-free periods because they are associated with improved health-related quality of life [25–27]. In oncology, important treatment goals include medication-free periods associated with symptom control, especially when there is a treatment-related toxicity or financial burden associated with treatment changes or combination therapy [25–27].

The TFI is not extensively studied in benign chronic diseases like IBS-D, where a prolonged TFI may suggest effective symptom management for patients through sustained periods with no IBS-D prescription medication. The exact pathophysiology of IBS-D is an area of active investigation. Studies in patients with gastrointestinal diseases such as IBS, ulcerative colitis, or Crohn's disease have shown that rifaximin increases the abundance of beneficial intestinal bacterial without altering overall gut microbial composition [28]. The longer TFI for rifaximin than eluxadoline in the present study may reflect a temporary or potentially permanent disease modification in the rifaximin cohort and improved patient outcomes, thereby supporting the TFI as a potential novel measure of treatment effectiveness in IBS-D. The TFI can be readily assessed using claims data, where consistent definitions for comparators and easily modifiable thresholds can be applied to assess different periods of time in which patients remain treatment-free. Considering the difficulty in controlling IBS-D symptoms, future studies are warranted to assess the value of the TFI in IBS-D and other chronic conditions.

In this study, over a 1-year period, nearly half of the patients who initiated rifaximin achieved a TFI of at least 8 months compared to less than a third of patients who initiated eluxadoline. Additionally, 56.6% of patients who achieved a TFI of $\geq$ 30 days after initiating rifaximin did not fill another prescription for any IBS-D treatment during the study period compared to 42.7% of patients who initiated eluxadoline, suggesting that symptoms among patients treated with rifaximin were better managed and did not require further treatment compared to eluxadoline.

In addition to remaining treatment-free for longer periods of time, treatment with rifaximin was associated with cost savings compared to eluxadoline. On the basis of published wholesale acquisition costs from the *RedBook*, a 14-day course of rifaximin (550 mg thrice daily) costs $1707 and a 30-day course of eluxadoline (100 mg twice daily) costs $1601. This study considered costs incurred from a payer's perspective, which included not only the cost of the medication but also all other treatments and medical services incurred by the patients over the study period, providing a

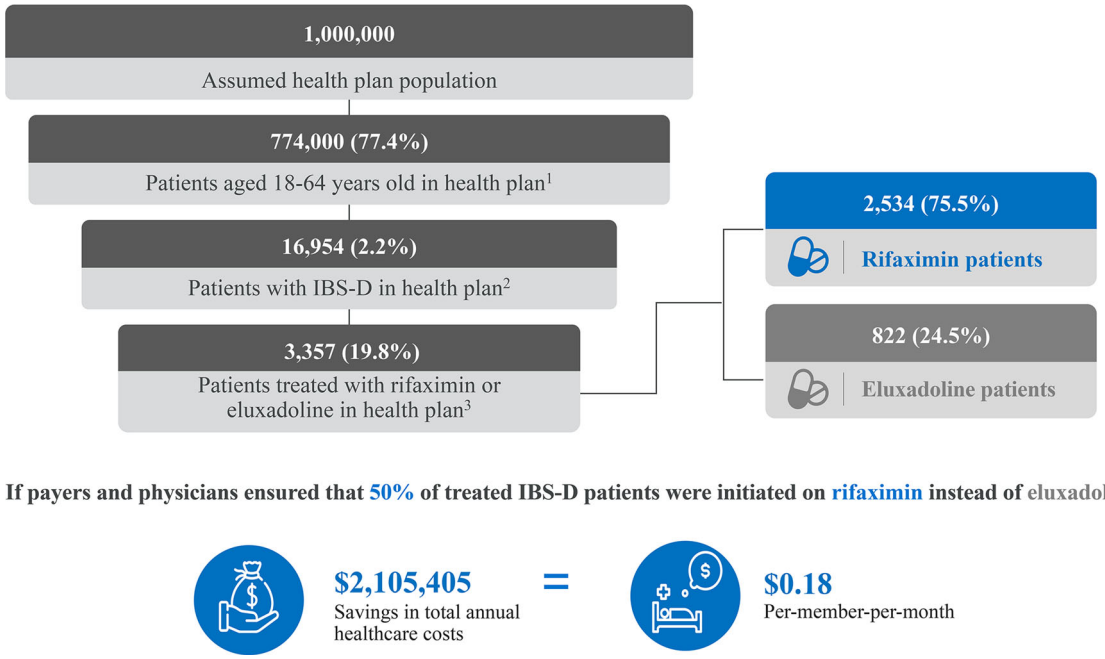

Fig. 5 Impact of patients with IBS-D initiating treatment with rifaximin instead of eluxadoline in a simulated health plan of one million commercially insured lives. [1]US Census Bureau, 2021 American Community Survey (ACS). Table HI05_ACS. Health Insurance Coverage Status and Type of Coverage by State and Age for All Persons 2021; Available at https://www.census.gov/data/tables/time-series/demo/health-insurance/acs-hi.html; Accessed on 15 Mar, 2023. The proportion is calculated on the basis of the total number of individuals that are only covered by private health insurance. Individuals that are covered by both private health insurance and public health insurance (i.e., Medicare and/or Medicaid) are excluded. [2]Almario et al., 2021. Prevalence and burden of illness of Rome IV irritable bowel syndrome in the U.S. DDW ePoster library; Available at https://eposters.ddw.org/ddw/2021/ddw-2021-virtual/319230/christopher.almario.prevalence.of.bowel.disorders.in.multiple.sclerosis.and.html?f=listing%3D4%2Abrowseby%3D8%2Asortby%3D2%2Amedia%3D2%2Aspeaker%3D851299; Accessed on 15 Mar, 2023. [3]Proportions were applied on the basis of analyses in PharMetrics® Plus (IQVIA) database claims data, which may not be representative of the total. *IBS-D* irritable bowel syndrome with diarrhea

comprehensive view of their healthcare costs. From this perspective, patients who initiated rifaximin incurred an average of $5120 less healthcare costs PPPY compared with those who initiated eluxadoline. The cost reduction was largely driven by lower pharmacy costs, which were $2902 lower PPPY with rifaximin than with eluxadoline. These cost savings are potentially associated with patients achieving an earlier treatment response when treated with rifaximin than with eluxadoline, as identified by the greater proportion of patients achieving TFIs across all time points assessed. Medical costs were also $2218 lower PPPY among patients treated with rifaximin compared to eluxadoline, although the difference was not significant. The observed cost differences could be attributed to patients experiencing a superior, and potentially more sustainable, response with rifaximin compared with eluxadoline, thus requiring less frequent treatments and fewer medical visits within a 1-year time frame. Additional studies are warranted to further explore these findings.

From the perspective of a commercial health insurance plan of one million members, if payers and physicians ensured that 50% of eluxadoline-treated patients with IBS-D were initiated on rifaximin instead of eluxadoline, overall cost savings may potentially amount to $2.1 million annually, or $0.18 PMPM, based on the annual per-patient healthcare cost savings

observed in this study. The benefits demonstrated by rifaximin in this study may provide substantial practical advantages when considered on a large scale, such that rifaximin treatment of patients with IBS-D could yield long-term economic benefits.

All-cause cost estimations presumed balanced cohorts following entropy balancing, which aimed to harmonize baseline characteristics between the rifaximin and eluxadoline cohorts. Accordingly, to account for any comorbidities that may be present more in one cohort compared to the other, diagnosis codes observed during the baseline period were tabulated, and any condition with > 10% frequency in the rifaximin cohort with an absolute standardized difference > 0.2 was included in the balancing. Any other measured comorbidities exceeding these thresholds were considered unlikely to influence the results because of low prevalence and minimal imbalance. Despite inherent limitations of real-world data, extensive comorbidity adjustment was performed, which included consultation with a clinical expert, to mitigate potential confounding and maximize comparability between cohorts.

Notably, approximately one-third of the patients included in this study received a corticosteroid sometime during the 12-month baseline period. As corticosteroids are not standard of care for IBS, their use in these patients is unlikely to be related to this condition. Corticosteroids are used for a variety of reasons (e.g., asthma, allergies, arthritis, hives, allergic reaction to a medication), which were not the focus of the current study. Additionally, the reasons patients received corticosteroids cannot be confirmed because of the nature of claims data. However, the presence of common diagnoses in the data, including joint pain, respiratory infections, and asthma, suggest potential indications for corticosteroid use in this population. Entropy balancing effectively adjusted for potential confounding by corticosteroid use, given similar usage between cohorts and minimal differences (i.e., aSD > 0.2) in the frequency of associated conditions. Consequently, corticosteroid use is unlikely to influence the findings.

The findings from this study should be interpreted in light of some limitations. The study focused on a commercially insured population and the findings may not be generalizable to all patients with IBS-D in the USA. Additionally, despite applying balancing techniques to ensure comparable patient cohorts, differences in unmeasured patient characteristics unavailable in administrative claims data, such as disease severity, may have remained. As with all claims-based studies, the data used in the study may have included billing inaccuracies or omissions in coded procedures, diagnoses, and pharmacy claims. These analyses were also limited to information available in the administrative claims data and, as such, data on use of over-the-counter medication were not available and TFI analyses considered prescription medications only. Lastly, only paid claims from insurance providers were captured in this analysis.

CONCLUSION

The TFI is a meaningful measure that can be used as a proxy for measuring treatment effectiveness in patients with IBS-D, and provides a novel approach to comparing treatments in real-world claims data. The results of this study demonstrated that patients with IBS-D may benefit more from treatment with rifaximin compared to eluxadoline by allowing them to stay treatment-free for longer periods, potentially suggesting an earlier and more sustained treatment response. In addition, rifaximin treatment resulted in lower healthcare costs compared with eluxadoline, indicating potential cost savings associated with improved treatment effectiveness when patients with IBS-D are treated with rifaximin in clinical settings.

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Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available as they are subject to Health Insurance Portability and Accountability Act privacy restrictions.

Declarations

Conflict of Interest. Brian E. Lacy has served as a consultant or served on scientific advisory boards to Bausch Health US, LLC, Salix Pharmaceuticals, Inc., Ironwood Pharmaceuticals, Inc., Abbvie, Inc., Gemelli Biotech, and Sanofi S.A. Zeev Heimanson, Brock Bumpass, and Ankur A. Dashputre are employees of Bausch Health US, LLC. Danellys Borroto was a Rutgers Institute for Pharmaceutical Industry Fellow at Bausch Health US, LLC at the time the study was conducted. George Joseph was an employee of Bausch Health US, LLC when the study was conducted and is currently employed by BioNTech US Inc. Patrick Gagnon-Sanschagrin, Rebecca Bungay, Remi Bellefleur, and Annie Guérin are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to Bausch Health US, LLC, which funded the development and conduct of this study and manuscript.

Ethical Approval. Data are de-identified and comply with the requirements of the Health Insurance Portability and Accountability Act; therefore, institutional review board exemption or informed consent was not required.

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