Safety and tolerability of rifaximin for the treatment of irritable bowel syndrome without constipation: a pooled analysis of randomised, double-blind, placebo-controlled trials

P. Schoenfeld*, M. Pimentel†, L. Chang‡, A. Lembo§, W. D. Chey*, J. Yu*, C. Paterson‖, E. Bortey* & W. P. Forbes

*University of Michigan School of Medicine, Ann Arbor, MI, USA.
†Cedars-Sinai Medical Center, Los Angeles, CA, USA.
‡David Geffen School of Medicine at UCLA, Los Angeles, CA, USA.
§Beth Israel Deaconess Medical Center, Boston, MA, USA.
‖Salix Pharmaceuticals, Inc., Raleigh, NC, USA.

Correspondence to:
Dr P. Schoenfeld, University of Michigan, Room 111D, 2215 Fuller Road, Ann Arbor, MI 48105, USA.
E-mail: pschoenf@umich.edu

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SUMMARY

Background
The efficacy of rifaximin, a nonsystemic, gut-targeted antibiotic for reducing non–constipation-predominant irritable bowel syndrome (non-C IBS) symptoms, has been demonstrated in one phase 2b and two phase 3 randomised, double-blind, placebo-controlled trials, but detailed data about rifaximin safety and tolerability during treatment and subsequent follow-up periods are lacking.

Aim
To assess and determine the frequency of rifaximin and placebo adverse events (AEs) in phase 2b and phase 3 non-C IBS trials.

Methods
A post hoc pooled safety analysis of the phase 2b (rifaximin 275, 550, and 1100 mg twice daily for 2 weeks; 550 mg twice daily for 4 weeks) and phase 3 (rifaximin 550 mg three times daily for 2 weeks) studies was performed. Data on treatment and post-treatment AEs were collected. Patients were followed up for 12 weeks and 10 weeks post-treatment in the phase 2b and phase 3 trials, respectively.

Results
Patients receiving rifaximin (n = 1103) and placebo (n = 829) had a similar incidence of drug-related AEs (12.1% vs. 10.7%), serious AEs (1.5% vs. 2.2%), drug-related AEs resulting in study discontinuation (0.8% vs. 0.8%), gastrointestinal-associated AEs (12.2% vs. 12.2%) and infection-associated AEs (8.5% vs. 9.5%). There were no cases of Clostridium difficile colitis or deaths.

Conclusions
The safety and tolerability profile of rifaximin during treatment and post-treatment was comparable to placebo. Future research should define the safety and tolerability profile, including risk of C. difficile colitis and microbial antibiotic resistance, with repeated courses of rifaximin in patients with non—constipation-predominant irritable bowel syndrome (ClinicalTrials.gov: NCT00269412, NCT00731679, and NCT00724126).
INTRODUCTION

Irritable bowel syndrome (IBS) manifests as abdominal pain and discomfort and altered bowel function, ranging from diarrhoea-predominant IBS (IBS-D) to constipation-predominant IBS (IBS-C), in the absence of biochemical or structural pathology. Patients are generally considered to have IBS-D when their bowel movements contain loose or watery stools ≥25% of the time and they experience hard or lumpy stools <25% of the time, while patients with IBS-C generally have hard or lumpy stools >25% of the time and loose, watery stools <25% of the time.

Irritable bowel syndrome has a substantial negative impact on patient quality of life and may affect between 1% to more than 20% of adults (depending on disease definition and global geographical location). Furthermore, IBS is one of the most common conditions managed by primary care physicians and gastroenterologists worldwide. Therefore, development of effective, well-tolerated and safe IBS treatments is important. However, available IBS therapies have limited efficacy, while some conventional IBS therapies are poorly tolerated in some patients (e.g., fibre products are more likely than placebo to produce bloating, and anti-spasmodics are more likely than placebo to produce anti-cholinergic adverse effects).

The pathophysiology of IBS is believed to be multifactorial, and there is increasing evidence that small intestinal bacterial overgrowth and changes in colonic microflora may lead to IBS symptoms in some patients. Therefore, antibiotics have been proposed as a possible treatment for IBS, and multiple randomised controlled trials (RCTs) have assessed the efficacy of rifaximin (Xifaxan; Salix Pharmaceuticals, Inc., Raleigh, NC, USA). Rifaximin is a nonsystemic oral antimicrobial agent that is targeted to the gastrointestinal tract. Rifaximin is currently indicated for the treatment of travelers’ diarrhoea caused by non-invasive strains of Escherichia coli in patients aged ≥12 years and for decreasing the risk of overt hepatic encephalopathy (HE) recurrence in adults. Rifaximin is in clinical development in the United States for the treatment of IBS-D, although it has been studied in combined populations of IBS-D and mixed-IBS, which has been characterised as non–constipation-predominant IBS (non-C IBS).

Two identically designed, randomised, double-blind, placebo-controlled, phase 3 trials (TARGET 1 and TARGET 2) demonstrated that patients with non-C IBS receiving rifaximin 550 mg three times daily for 2 weeks were more likely to achieve adequate relief of global IBS symptoms than those receiving placebo (40.7% vs. 31.7%, respectively; P < 0.001), as well as adequate relief of IBS–related bloating (40.2% vs. 30.3%, P < 0.001) during ≥2 of the first 4 weeks post-treatment compared with placebo. Furthermore, a significantly greater percentage of patients treated with rifaximin experienced adequate relief of global symptoms of IBS throughout the 12-week studies (2 weeks of treatment and 10 weeks of follow-up). A phase 2b dose-ranging study also demonstrated efficacy of rifaximin vs. placebo in patients with non-C IBS. In addition, a third phase 3 RCT (TARGET 3), assessing the efficacy and safety of repeated courses of rifaximin 550 mg three times daily for the management of IBS-D, is currently ongoing.

Because less than 1% of rifaximin is absorbed systemically, the drug may be well tolerated with fewer systemic adverse events. However, development of Clostridium difficile colitis and antimicrobial resistance are appropriate concerns when antibiotics are used, especially because long-term management of IBS with rifaximin may require repeated courses of treatment. Although the phase 2b and phase 3 RCTs did not address antibiotic microbial resistance, these RCTs did collect detailed safety and tolerability data that have not been previously published. The objective of the current analysis was to conduct a pooled safety and tolerability assessment of rifaximin compared with placebo in the treatment of IBS using data from the phase 2b and phase 3 trials.

METHODS

Study design and patient population

Data were pooled from one phase 2b (NCT00269412) trial and two phase 3, double-blind, placebo-controlled trials (NCT00731679 and NCT00724126) conducted in the United States and Canada. Information on the study design and patient population for the two phase 3 trials has been previously published. In all three trials, patients were ≥18 years of age and had a confirmed diagnosis of IBS using Rome II criteria and met criteria for non-C IBS. The phase 2b and phase 3 trials excluded patients with symptoms of constipation during the ≥7-day eligibility period. All phase 2b and phase 3 trial protocols were approved by the institutional review board or independent ethics committee for each study site and all patients provided informed written consent.

In all three studies, the randomisation code was computer generated and stratified by centre. Patients in the phase 2b trial were randomised (2:1:2:1:1) to receive one of the five following regimens: placebo twice daily for 4 weeks; rifaximin 275 mg twice daily for 2 weeks,
followed by placebo for 2 weeks; rifaximin 550 mg twice daily for 2 weeks, followed by placebo for 2 weeks; rifaximin 1100 mg twice daily for 2 weeks, followed by placebo for 2 weeks; or rifaximin 550 mg twice daily for 4 weeks. Patient follow-up visits were conducted post-treatment for 12 weeks (i.e., 16-week study period). Patients in the phase 3 trials were randomised (1:1) to receive rifaximin 550 mg three times daily or placebo three times daily for 2 weeks and followed 10 weeks post-treatment (i.e., 12-week study period).

Safety assessments
Safety parameters that were assessed in the studies included overall adverse events (AEs), AEs resulting in discontinuation from the study, serious AEs, gastrointestinal-associated AEs, and infection-associated AEs. The AEs were treatment-emergent and defined as any AE occurring on or after Day 1 of treatment (or, for pre-existing conditions, worsening on or after Day 1). A patient who had more than one incident of the same AE was counted once for that event, according to the most severe intensity of the event or the closest relationship with treatment.

Analysis of pooled AE data was performed for the overall evaluation period [treatment (2 or 4 weeks) plus post-treatment (10 or 12 weeks) periods] and for the treatment period only. AE severity was classified as mild, moderate, severe, or not applicable. An AE was considered serious if life-threatening or resulting in death; in-patient hospitalisation; or prolongation of existing hospitalisation, disability or incapacity, congenital anomaly, or other event considered serious, based upon appropriate medical judgment.

In the phase 2b trial, AE data were collected and measured at randomisation and at weeks 1, 2, 4, 6, 8, 12, and 16; laboratory tests (i.e., blood chemistry, haematology, and urinalysis) were performed during screening and at weeks 2 and 4; and physical examinations were performed during screening and at week 4. Data on AEs in the phase 3 trials were recorded at screening and baseline and at weeks 1, 2, 4, 6, 8, 10, and 12. Physical examinations and laboratory tests (i.e., blood chemistry, haematology, urinalysis) were conducted at screening and at weeks 2 and 12.

Statistical analyses
Safety data from the three trials were pooled and analysed for all patients who received ≥1 dose of study medication and included at least 1 post-baseline safety assessment (safety population). Descriptive statistics were used, with categorical variables summarised using counts and percentages and continuous variables summarised using mean, standard deviation, minimum, and maximum.

RESULTS

Demographics
A total of 1940 patients were enrolled in the one phase 2b and two phase 3 rifaximin trials, and 1932 patients were included in the safety population. Of these patients, 674 were treated in the phase 2b trial (479 treated with rifaximin and 195 treated with placebo), and 1258 were treated in the two phase 3 trials (624 treated with rifaximin and 634 treated with placebo). Overall, approximately 89% of the patients were aged <65 years, and the mean age was 46 years (Table 1). Approximately 73% of the patients were female and approximately 92% of patients were white. One hundred per cent of the patients in the phase 3 rifaximin trials and 78% of the patients in the phase 2b trial met criteria for IBS-D.

Safety
During the overall evaluation period (treatment phase and post-treatment follow-up), the majority of AEs were mild to moderate in intensity for both the rifaximin and placebo groups. The overall safety profile with rifaximin, for both the all-rifaximin and the 550-mg pooled groups, was comparable to the safety profile for placebo (Table 2). The incidence of any AEs, AEs considered by the investigator to be drug-related, serious AEs and AEs resulting in study discontinuation were similar between both groups. No deaths occurred during the trials, and none of the reports of serious AEs included ischaemic colitis or constipation. There were no clinically significant changes from baseline in laboratory test findings in the rifaximin-treated and placebo-treated patients.

The most common AEs experienced during the overall evaluation period by patients in the rifaximin group (pooled) and the placebo group, respectively, included those associated with the gastrointestinal tract or with infection, with upper respiratory tract infection and nausea reported most often in the pooled rifaximin group (Table 2). Because gastrointestinal- and infection-associated AEs were among the most common, an analysis of gastrointestinal- and infection-associated AEs by rifaximin dosage during the treatment period was conducted. The incidence of gastrointestinal- and infection-associated AEs occurring in ≥1% of patients was similar across the range of rifaximin dosages and was comparable to that
for placebo (Table 3). Among patients treated with rifaximin 550 mg three times daily, 10.9% experienced a gastrointestinal-associated AE during treatment; nausea, abdominal pain, and flatulence were most frequently reported. This group also had the lowest reported incidence of infection-associated AEs (5.1%) during treatment compared with the other dosage groups, as well as compared with the pooled rifaximin analysis.

In the IBS population overall, one patient had a *C. difficile*–positive stool culture at baseline; this patient received study medication (rifaximin 550 mg twice daily) until positive test results were obtained, prompting withdrawal from the study due to the exclusion criteria (positive baseline stool culture result) being met. However, no patient developed *C. difficile* colitis, as determined via stool testing during active treatment. Therefore, the rate of *C. difficile* colitis in the overall IBS population was zero (no cases per 61.3 patient-years of exposure).

The incidence of constipation was low during the treatment period for patients receiving rifaximin (0.7%, pooled) and placebo (1.1%), as well as during the overall evaluation period [rifaximin (1.4%, pooled) and placebo (1.3%)] and during the overall evaluation period [rifaximin (3.4%, pooled) and placebo (3.1%)].

**DISCUSSION**

Rifaximin is a nonsystemic, gastrointestinal-targeted antibiotic under clinical development for the treatment of IBS. Per the American College of Gastroenterology evidence-based position statement on the management of IBS, ’a short-term course of a non-absorbable antibiotic is more effective than placebo for global improvement of IBS and for bloating’. The position statement also noted ’minimal safety data were reported...but rifaximin-treated patients reportedly tolerated antibiotics without severe adverse events’. Therefore, to better understand the safety and tolerability of rifaximin for the treatment of IBS, a pooled safety analysis of phase 2b and phase 3 trials was conducted. These data represent the most comprehensive report about the safety and tolerability of rifaximin in patients with IBS.

The incidence of all AEs, serious AEs, drug-related AEs, AEs leading to study discontinuation, gastrointestinal-associated AEs, and infection-associated AEs with rifaximin was comparable to placebo during the overall evaluation period [rifaximin (1.4%, pooled) and placebo (1.3%)] and during the overall evaluation period [rifaximin (3.4%, pooled) and placebo (3.1%)].
evaluation period and during the treatment period. No apparent dose-related increase in gastrointestinal-associated AEs or risk for infection emerged from the analysis. Gastrointestinal-associated AEs were reported in 13.7% of patients in the lowest rifaximin dose group and in 16.3% of patients in the highest rifaximin dose group. Infection-associated AEs occurred in 16.8% of patients in the lowest dose group and in 15.3% in the highest dose group. No clear dose-related increase in individual gastrointestinal-associated or infection-associated AEs was observed. This safety and tolerability profile may result from the low systemic absorption (<1%) of rifaximin.

These results are consistent with a published meta-analysis of 5 double-blind, placebo-controlled trials\(^5\) and additional smaller, prospective trials in which rifaximin for the treatment of IBS was well tolerated.\(^12\)–\(^15\) In these studies, the incidence of AEs with rifaximin was low, with no statistically significant differences in AEs for rifaximin-treated patients vs. placebo-treated patients. Our study provides a more comprehensive analysis by pooling data from the three largest RCTs, while also providing data about additional individual adverse events. The similarity in the incidence, intensity and type of AEs reported for the rifaximin and placebo groups in the current analysis supports the use of rifaximin in this patient population when its short-term safety and tolerability profile is considered.

The chronic nature of IBS typically necessitates long-term management strategies. In the case of rifaximin, many patients may require repeated courses of rifaximin and concerns have been raised about the risk of development of *C. difficile* infection with antimicrobial therapy.\(^16\) Therefore, additional descriptive data and pooled analyses from RCTs were performed to assess frequency of *C. difficile* colitis cases per patient-years of exposure in multiple patient populations, including: (i) IBS; (ii) HE using RCT and long-term open-label maintenance/safety study data; and (iii) Crohn’s disease. In a single phase 2 RCT of Crohn’s disease, 308 patients received 800–2400 mg/day of rifaximin extended intestinal release for up to 12 weeks, totalling 59.2 patient-years of exposure.\(^17\) One case of *C. difficile* colitis was diagnosed in a patient treated with rifaximin extended intestinal release 1600 mg/day at 20 days post-treatment. Therefore, in the Crohn’s disease population, the rate of *C. difficile* colitis was 1.7 events per 100 patient-years of exposure. Treatment of HE with rifaximin has been studied in a 6-month randomised, double-blind, placebo-controlled trial\(^18\) and in a long-term (>3 years) open-label maintenance trial of rifaximin 550 mg twice daily for the prevention of HE recurrence.\(^19\)–\(^20\) In the RCT of patients with cirrhosis and a history of HE, two cases of *C. difficile* colitis were diagnosed, and another four cases were diagnosed during the long-term open-label maintenance study. Thus, six cases of *C. difficile* colitis were diagnosed in 508.5 patient-years of exposure, corresponding to a rate of 1.2 events per 100 patient-years of exposure in the HE population. Because patients with HE may be continuously exposed to rifaximin to prevent disease recurrence, are frequently hospitalised, and have multiple risk factors for this condition, rates of *C. difficile* colitis are expected to be higher for patients with HE than for patients with IBS. It should also be noted that rifaximin has potent activity against most *C. difficile* strains and has been investigated as a potential treatment option.\(^21\)–\(^26\)

Concerns about development of microbial antibiotic resistance with widespread and recurrent use of rifaximin are understandable, although development of resistance may be small, due to the mechanism of antibiotic resistance with rifaximin. With many antibiotics, resistance is transmitted by mobile genetic elements, such as plasmids or transposons, which facilitate rapid development of antibiotic resistance among a population of bacteria. Antibiotic resistance to rifaximin appears to occur through chromosomal mutation that blocks the ability of the agent to inhibit bacterial DNA-dependent RNA polymerase, and these mutations are rare.\(^27\) In patients treated with rifaximin for 5 days, resistant bacterial strains were recovered, but susceptibility to rifaximin was regained 1–12 weeks after treatment discontinuation.\(^28\) Also, in a placebo-controlled trial, no significant increases in antimicrobial resistance in Gram-positive or Gram-negative bacteria were observed in patients treated with rifaximin compared with patients receiving placebo for 3 days.\(^29\) However, antibiotic resistance in patients receiving rifaximin for the treatment of other gastrointestinal diseases has been described.\(^30\), \(^31\)

There are a number of limitations of the current analysis. For example, patients were treated with only a single course of therapy, although management of rifaximin for IBS will most likely require repeated courses of treatment. Also, 100% of the patients in the phase 3 studies and 78% of the patients in the phase 2b trial met criteria for IBS-D, so these data may be more applicable to an IBS-D population instead of the non-C IBS population. Additional limitations include: a risk of potential bias of pooling data from phase 2 and phase 3 studies with varied design, the small number of patients included in the lower rifaximin dosage groups, the limited extent of drug exposure, and the lack of
minimum inhibitory concentration assessments of bacterial strains isolated from rifaximin-exposed patients. The ongoing TARGET 3 (retreatment) trial has measures included in its study design that will help quantify rates of microbial antibiotic resistance and disappearance in bacterial strains isolated from patients with IBS who have been exposed to multiple courses of rifaximin.11

In summary, under the conditions studied, rifaximin appears to be safe and well tolerated in the treatment of non-C IBS – with no increased risk of infections, including C. difficile infection and no substantial differences in any AEs vs. placebo. This profile would be a major benefit of rifaximin for treatment of IBS when used in appropriate subgroups of patients.

AUTHORSHIP

Guarantor of the article: W.P. Forbes.

Author contributions: Dr Schoenfeld contributed to clinical trial study design, analysed data and wrote and edited the manuscript. Dr Pimentel, Dr Chang, Dr Lembo, Dr Chey, Dr Yu, Dr Bortey and Dr Forbes critically reviewed the clinical trial study design, analysed data and critically reviewed and edited the manuscript. Dr Paterson analysed data and critically reviewed and edited the manuscript. All authors approved the final version of the manuscript.

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| Table 2 | Overall evaluation period adverse event profile |
| Adverse event | Patients, n (%) |
|---------------|----------------|
|                | All-rifaximin (pooled) (n = 1103) | Rifaximin 550 mg (pooled) (n = 1008) | Placebo (n = 829) |
| Any AE         | 579 (52.5) | 529 (52.5) | 436 (52.6) |
| Specific AE in ≥2% of patients* |
| Headache       | 59 (5.3)  | 55 (5.5)  | 51 (6.2)  |
| URTI           | 50 (4.5)  | 45 (4.5)  | 47 (5.7)  |
| Nausea         | 48 (4.4)  | 41 (4.1)  | 31 (3.7)  |
| Abdominal pain | 41 (3.7)  | 40 (4.0)  | 39 (4.7)  |
| Diarrhoea      | 37 (3.4)  | 35 (3.5)  | 26 (3.1)  |
| UTI            | 37 (3.4)  | 32 (3.2)  | 18 (2.2)  |
| Nasopharyngitis| 26 (2.4)  | 26 (2.6)  | 39 (4.7)  |
| Sinusitis      | 24 (2.2)  | 23 (2.3)  | 23 (2.8)  |
| Vomiting       | 22 (2.0)  | 20 (2.0)  | 12 (1.4)  |
| Back pain      | 22 (2.0)  | 20 (2.0)  | 19 (2.3)  |
| AE severity†   |
| Mild           | 268 (24.3) | 244 (24.2) | 169 (20.4) |
| Moderate       | 246 (22.3) | 225 (22.3) | 214 (25.8) |
| Severe         | 63 (5.7)   | 58 (5.8)   | 53 (6.4)   |
| Drug-related AEs | 134 (12.1) | 124 (12.3) | 89 (10.7)  |
| Serious AEs    |
| Any serious AE | 16 (1.5)   | 15 (1.5)   | 18 (2.2)   |
| Drug-related serious AEs | 1 (0.1) | 1 (0.1) | 2 (0.2) |
| Deaths         | 0          | 0          | 0          |
| AEs resulting in study discontinuation |
| Any AE         | 22 (2.0)  | 19 (1.9)  | 14 (1.7)  |
| Drug-related AE | 9 (0.8)   | 9 (0.9)   | 7 (0.8)   |

AE, adverse event; URTI, upper respiratory tract infection; UTI, urinary tract infection.

* Occurring in ≥2% of patients in either rifaximin group or in placebo group.
† Data not available for 2 AEs in rifaximin groups.
Table 3 | Treatment period gastrointestinal and infection-associated adverse events experienced by ≥1% of patients

| Patients, n (%) | Rifaximin |
|----------------|-----------|
|                | 275 mg twice daily | 550 mg twice daily | 550 mg twice daily | 550 mg three times daily | 1100 mg twice daily | Pooled | Placebo |
| Adverse event  | 2 weeks (n = 95) | 2 weeks (n = 190) | 4 weeks (n = 96) | 2 weeks (n = 624) | 2 weeks (n = 98) | (n = 1103) | (n = 829) |
| GI-associated AEs | | | | | | | |
| Any GI-associated AE | 13 (13.7) | 29 (15.3) | 9 (9.4) | 68 (10.9) | 16 (16.3) | 135 (12.2) | 101 (12.2) |
| Nausea | 5 (5.3) | 6 (3.2) | 3 (3.1) | 16 (2.6) | 4 (4.1) | 34 (3.1) | 19 (2.3) |
| Abdominal pain | 1 (1.1) | 3 (1.6) | 1 (1.0) | 17 (2.7) | 4 (4.1) | 26 (2.4) | 21 (2.5) |
| Flatulence | 2 (2.1) | 3 (1.6) | 0 | 9 (1.4) | 4 (4.1) | 18 (1.6) | 14 (1.7) |
| Diarrhoea | 1 (1.1) | 1 (0.5) | 2 (2.1) | 9 (1.4) | 2 (2.0) | 15 (1.4) | 11 (1.3) |
| Vomiting | 1 (1.1) | 1 (0.5) | 3 (3.1) | 6 (1.0) | 1 (1.0) | 12 (1.1) | 5 (0.6) |
| Abdominal distension | 1 (1.1) | 1 (0.5) | 1 (1.0) | 7 (1.1) | 2 (2.0) | 12 (1.1) | 3 (0.4) |
| Constipation | 0 | 3 (1.6) | 1 (1.0) | 4 (0.6) | 0 | 8 (0.7) | 9 (1.1) |
| Infection-associated AEs | | | | | | | |
| Any infection-associated AE | 16 (16.8) | 22 (11.6) | 9 (9.4) | 32 (5.1) | 15 (15.3) | 94 (8.5) | 79 (9.5) |
| UTI | 4 (4.2) | 6 (3.2) | 2 (2.1) | 3 (0.5) | 4 (4.1) | 19 (1.7) | 7 (0.8) |
| URTI | 4 (4.2) | 4 (2.1) | 0 | 4 (0.6) | 2 (2.0) | 14 (1.3) | 19 (2.3) |
| Nasopharyngitis | 0 | 2 (1.1) | 0 | 4 (0.6) | 2 (2.0) | 8 (0.7) | 20 (2.4) |
| Sinusitis | 0 | 2 (1.1) | 1 (1.0) | 1 (0.2) | 0 | 4 (0.4) | 8 (1.0) |

AE, adverse event; GI, gastrointestinal; URTI, upper respiratory tract infection; UTI, urinary tract infection.

Declaration of personal interests: Dr Schoenfeld is a consultant, advisory board member, and member of the speakers’ bureaus of Salix Pharmaceuticals, Inc., Ironwood Pharmaceuticals, Inc., and Forest Laboratories, Inc. He is also a partner in MD-Evidence, LLC, a medical education and consulting company. Dr Pimentel has served as a consultant for and has received research grants from Salix Pharmaceuticals, Inc. He reports that Cedars-Sinai Medical Center holds patents licensed by Salix Pharmaceuticals, Inc. Dr Chang has served as an advisory board member and consultant for Salix Pharmaceuticals, Inc., Ironwood Pharmaceuticals, Inc., Forest Laboratories, Inc., Takeda, and Purdue Pharma L.P. She has received research grants from Ironwood Pharmaceuticals, Inc. Dr Lembo has served as an advisory board member and consultant for Salix Pharmaceuticals, Inc., Ironwood Pharmaceuticals, Inc., Forest Laboratories, Inc, and Prometheus Labs. Dr Chey has served as a consultant for AstraZeneca, Asubio, Forest, Ironwood, Nestle, Perrigo, Prometheus, Salix, SK, Sucampo and Takeda. He has received research grants from Ironwood, Perrigo and Prometheus. Drs Yu, Paterson and Bortey are employees of Salix and own stock and shares in Salix. Dr Forbes is an employee of Salix and owns stock and shares in Salix.

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