Common Drug Review
Clinical Review Report

July 2015

Drug	rifaximin (Zaxine) (550 mg tablet)
Indication	For the reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥ 18 years of age.
Listing request	For patients who are unable to achieve adequate disease control, i.e. controlling HE recurrence, with lactulose alone, or for patients who are at risk of recurrent HE who are unable to tolerate lactulose.
Manufacturer	Salix Pharmaceuticals Inc.

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

AE	adverse event
CDR	CADTH Common Drug Review
CI	confidence interval
CLF	Canadian Liver Foundation
CLDQ	Chronic Liver Disease Questionnaire
DB	double-blind
FDA	US Food and Drug Administration
GI	gastrointestinal
HE	hepatic encephalopathy
HR	hazard ratio
HRQoL	health-related quality of life
ITT	intention-to-treat (population)
MELD	Model End-stage Liver Disease
MCID	minimal clinically important difference
OLM	open-label maintenance (trial)
PYE	person-years of exposure
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SF-36	Short-Form 36-item Health Questionnaire
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Hepatic encephalopathy (HE) is a complication of various forms of liver disease, most notably cirrhosis. There are no data on the prevalence of cirrhosis in Canada;[1] the manufacturer cited data estimating the prevalence of cirrhosis in the US at approximately 800,000 to 1 million. HE appears to result from the accumulation of toxic substances such as ammonia that are normally removed by the liver. It is characterized by neuropsychological deficits that can range from impaired cognitive performance and anxiety, to disorientation and personality changes, to stupor and confusion, and finally to coma and death. One of the more classic signs of HE is asterixis, a flapping tremor of the hand. Overt HE is defined based on the severity of impairment in mental status and neuromotor functioning (i.e., asterixis). Overt HE is estimated to occur in 28% to 43% of patients with cirrhosis, and it is second only to ascites among the common complications of cirrhosis. HE is responsible for one-third to one-half of hospitalizations related to cirrhosis.[2] HE is also seen in 10% to 50% of patients with transjugular intrahepatic portosystemic shunts (TIPS).[3]

The most common approach to preventing overt HE has traditionally been the administration of lactulose. Lactulose is a disaccharide that is not absorbed, but instead stays in the gut and is metabolized by gut bacteria into acidic compounds that alter the pH balance of the colon sufficiently to facilitate the excretion of ammonia. The main limitations of lactulose are its poor palatability and gastrointestinal (GI) adverse effects, particularly diarrhea.

Rifaximin is an orally administered, broad-spectrum antibiotic belonging to the rifamycin class that has activity against gram-positive, gram-negative, aerobic, and anaerobic enterobacteria, and it is poorly absorbed (< 1%) from the GI tract. The principal behind the use of rifaximin for HE is the elimination of the gut bacteria that are responsible for producing HE-causing toxins. Rifaximin is administered orally as a 550 mg tablet twice daily.

Indication under review
For the reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥ 18 years of age.
Listing criteria requested by sponsor
For patients who are unable to achieve adequate disease control, i.e. controlling HE recurrence, with lactulose alone, or for patients who are at risk of recurrent HE who are unable to tolerate lactulose.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of rifaximin for reducing the risk of overt HE recurrence in patients ≥ 18 years of age who are at risk of HE recurrence despite the use of lactulose, or who are intolerant to lactulose.

Results and Interpretation

Included Studies

Two double-blind (DB), randomized controlled trials (RCTs) met the inclusion criteria for this review, both comparing rifaximin 550 mg twice daily to placebo. Study 3001 (N = 299) was a manufacturer-sponsored, multinational, phase 3 pivotal trial that enrolled patients who had had at least two episodes of overt HE within the six months before randomization, and who were in remission from HE at baseline. Patients were randomized in an approximately 1:1 ratio to either rifaximin or placebo over a six-month treatment course. Most patients (> 90%) used lactulose at baseline and continued to use lactulose throughout the study. The other study, by Ali et al. (N = 126),[4] was a published, single-centre study conducted in Pakistan; it does not appear to have been supported by the manufacturer of rifaximin, and its methods and results were scantily reported. Hence, Study 3001 was the focus of this review. The primary outcome in Study 3001 was time to first breakthrough episode of overt HE, defined by changes in two symptom-scoring instruments used in HE: an increase (worsening) in Conn score (a 5-point scale that assesses neurocognitive function) to Grade 2 or higher, or an increase (worsening) of one grade in both the Conn score and the asterixis grade in patients with a Conn score of 0 at baseline. Key secondary outcomes in Study 3001 included time to HE-related hospitalization, time to increase in Conn score, time to increase in asterixis grade, and mean change from baseline in the fatigue domain of the Chronic Liver Disease Questionnaire (CLDQ), a disease-specific, health-related, quality-of-life instrument.

Based on clinical expert opinion and the requested listing criteria from the manufacturer, rifaximin is expected to be used in addition to lactulose for patients with inadequate control of HE despite optimal doses of lactulose alone, or as monotherapy for patients intolerant to lactulose. However, Study 3001 did not specifically enrol patients intolerant to lactulose; since more than 90% of patients used lactulose during the study, the generalizability of the results to patients using rifaximin as monotherapy is uncertain. Furthermore, among patients who used lactulose at baseline, it is uncertain to what extent attempts were made to optimize the dose of lactulose to maximize efficacy while maintaining an acceptable level of tolerability. The study by Ali et al. had numerous design and reporting issues that substantially limited the interpretability of results, and its setting (Pakistan) may limit its generalizability to Canadian clinical practice.

Efficacy

The primary outcome of Study 3001 was time to first breakthrough episode of overt HE. Rifaximin was statistically significantly superior to placebo for this outcome with a hazard ratio [HR] of 0.421 (95% confidence interval [CI], 0.276 to 0.641, $P < 0.0001$). Sensitivity analyses found that the results were similar upon exclusion of patients who had received concomitant medications other than lactulose for the prevention of HE, and of patients who had significant comorbidities that might increase the risk of developing overt HE. A subgroup analysis was performed comparing patients with and without prior lactulose use, although the findings were inconclusive due to the small number of patients who had not used lactulose. There were no data to inform whether there were differences in the severity or length of HE episodes between the rifaximin and placebo groups. More rifaximin-treated patients experienced improvements in Conn scores compared with placebo-treated patients, and this difference was statistically significant; however, there was no significant difference in asterixis scores between the rifaximin and placebo groups. Rifaximin was superior to placebo for hospitalizations related to HE, with an HR of 0.500 (95% CI, 0.287 to 0.873); however, neither duration of hospitalization nor all-cause hospitalizations were reported. A similar proportion of patients died in the rifaximin and placebo groups (7% in each) by the end of the six-month, DB treatment period.

Patient-group input received by the CADTH Common Drug Review (CDR) on this submission indicated that the impact of overt HE on quality of life is a significant concern for patients. In Study 3001, quality of life at the end of the study was not improved on CLDQ-fatigue for rifaximin versus placebo, although according to the manufacturer's hierarchical analysis plan this analysis was considered only exploratory. Similarly, none of the other domains on the CLDQ were improved for rifaximin versus placebo. However, a post hoc longitudinal re-analysis of the CLDQ data revealed that rifaximin was associated with statistically significant improvements in health-related quality of life (HRQoL) compared with placebo. Of note, the CLDQ was not administered during overt HE episodes, as patients were considered too incapacitated to complete the questionnaire at these times; this means that any quality of life gains due to reduced overt HE risk in the rifaximin group were not captured. Results for the Short-Form 36-item Health Questionnaire (SF-36) were also reported, but this was considered an exploratory outcome and no statistical analysis was provided.

Ali et al. reported that 16 patients in the rifaximin group and 14 patients in the placebo group had an overt HE episode. There was no statistically significant difference between treatment groups. There was also no apparent difference in the mortality rate between treatment groups.

Harms

Similar proportions of patients in the rifaximin and placebo groups (80% in each) experienced adverse events (AEs) by the end of the six-month, DB treatment period in Study 3001. Diarrhea occurred in 11% of rifaximin-treated patients and in 13% of patients in the placebo group. Hence, the addition of rifaximin to lactulose did not appear to increase the risk of diarrhea compared with lactulose alone. Other notable harms that occurred in 1% to 3% of patients included bacterial peritonitis, pneumonia, and GI hemorrhage. Serious adverse events (SAEs) were reported in 36% of rifaximin-treated patients and in 40% of placebo-treated patients. The most common SAEs were ascites (3% in each group) and hepatic cirrhosis (2% of rifaximin-treated patients and 4% of placebo-treated patients). Withdrawal due to adverse events (WDAEs) occurred in 21% of rifaximin-treated patients and 28% of placebo-treated patients; the most common reason for withdrawal was HE (reported by 10% of rifaximin-treated patients and 19% of placebo-treated patients).

Antimicrobial resistance is a potential concern when long-term antibiotic therapy is being considered. According to the manufacturer, resistance to rifaximin is not mediated by plasmids, which can be easily exchanged between organisms; therefore, the barrier to resistance may be higher than with other antibiotics used for HE prophylaxis. Resistance was not specifically reported as an outcome in Study 3001, and it is unlikely that the trial was of sufficient size or duration to meaningfully assess this outcome. Another concern associated with the use of broad-spectrum antibiotic therapy is the risk of opportunistic infection, particularly *Clostridium difficile*–associated diarrhea. The proportion of patients with diarrhea due to *C. difficile* was 1% with rifaximin and 0% with placebo in Study 3001. In an open-label extension of Study 3001 with follow-up of at least 24 months, the proportion of patients with *C. difficile* diarrhea remained less than 1%; hence, the risk did not appear to rise with extended treatment duration. Nevertheless, a warning about the risk of *C. difficile*–associated disease appears in the Product Monograph for rifaximin.

AE data were not reported in the study by Ali et al.; however, the authors noted that the incidence of AEs was similar between groups.

Other Considerations

Rifaximin is a mild inducer of CYP3A4, but no clinically significant interactions involving CYP3A4 were identified in healthy volunteers. However, rifaximin is a P-glycoprotein (Pgp) substrate, and concomitant use of rifaximin with potent Pgp inhibitors might lead to increased levels of rifaximin.[5]

Conclusions

Two DB RCTs met the inclusion criteria for this review, both comparing rifaximin 550 mg twice daily to placebo. Study 3001, a pivotal, manufacturer-sponsored, multi-centre phase 3 trial that enrolled 299 patients at risk of overt HE, provided the most reliable evidence and was the focus of the review. Rifaximin significantly reduced the risk of overt HE and HE-related hospitalization versus placebo in Study 3001. A similar proportion of patients died in the rifaximin and placebo groups. The effects of rifaximin on HRQoL were uncertain. Symptom scores were statistically significantly improved in rifaximin versus placebo on the Conn scale, but not on the asterixis scale. There were no apparent differences in the incidence of AEs or SAEs between groups. The proportions of patients with diarrhea were similar between the rifaximin and placebo groups. Data from an open-label extension study at up to 24 months' follow-up neither suggested new safety signals, nor an increased risk for previously observed AEs. There were insufficient data to determine the impact, if any, of rifaximin with respect to the risk of opportunistic infections or antimicrobial resistance. The risk of *C. difficile* infections was low in both treatment groups of Study 3001, and did not appear to increase in the open-label extension study.

Lactulose dosing was not necessarily optimized for maximal efficacy and tolerability at baseline in Study 3001, and patients intolerant to lactulose were not specifically included. These aspects potentially limit the generalizability of this study to Canadian clinical practice, as well as to the listing criteria requested by the manufacturer.

TABLE 1: SUMMARY OF RESULTS FROM STUDY 3001

Outcome	Study 3001	
	RIFAXIMIN N = 140	**PLACEBO N = 159**
BREAKTHROUGH HE[a]		
Events at 6 months	31	73
HR [95% CI]	0.421 [0.276 to 0.641]	
P value[b]	< 0.0001	
MORTALITY		
N (%)	10 (7)	11 (7)
Most common:		
Hepatic cirrhosis	0	4
Esophageal varices	3	2
HOSPITALIZATIONS, HE-RELATED		
Events at 6 months	19	36
Time to event, HR [95% CI]	0.500 [0.287 to 0.873]	
P value	0.0129	
QOL: CLDQ		
Overall score		
Mean (SD) baseline	4.12 (1.16)	4.15 (1.17)
Mean (SD) change from baseline to EOT	0.12 (0.87) N = 96	0.06 (1.08) N = 106
P value	0.2426	

Outcome	Study 3001	
	RIFAXIMIN N = 140	**PLACEBO N = 159**
Fatigue		
Mean (SD) baseline	3.28 (1.33)	3.34 (1.41)
Mean (SD) change from baseline to EOT	0.30 (1.26) N = 95	0.11 (1.32) N = 105
P value[c]	0.9877	
WITHDRAWALS (ALL-CAUSE)		
Total, n (%)	52 (37)	93 (59)
AEs		
Patients, n (%)	112 (80)	127 (80)
SAEs		
Patients, n (%)	51 (36)	63 (40)
WDAEs		
Patients, n (%)	30 (21)	45 (28)
Notable harm(s), patients, n (%)		
Diarrhea	15 (11)	21 (13)
Pneumonia	4 (3)	1 (1)
GI hemorrhage	1 (1)	3 (2)
Hematochezia	2 (1)	1 (1)
Bacteremia	1 (1)	2 (1)
Gastritis	2 (1)	0

AE = adverse event; CI = confidence interval; CLDQ = Chronic Liver Disease Questionnaire; EOT = end of therapy; GI = gastrointestinal; HE = hepatic encephalopathy; HR = hazard ratio; NR = not reported; QoL = quality of life; SD = standard deviation; SF-36 = Short-Form 36-item Health Questionnaire.

[a] "Time to first breakthrough overt HE episode" was defined as an increase of Conn score to Grade 2 or higher (i.e., Grade 0 or 1 to 2 or higher) or an increase in Conn score and asterixis grade of one grade each for those patients who entered the study with a Conn score of 0.

[b] HR estimates in the rifaximin group compared with the placebo group were determined from the Cox proportional hazards model with adjustment for region. *P* value were based on the Score statistic.

[c] Change from baseline in CLDQ-fatigue was a secondary outcome, but based on a hierarchical testing procedure this was an exploratory analysis. All other CLDQ outcomes were exploratory.

[d] *P* values were not reported for SF-36 data.

Source: Clinical Study Report for Study 3001.[6]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Hepatic encephalopathy (HE) is a key complication of liver cirrhosis. As a consequence of loss of function and shunting, the cirrhotic liver is no longer able to carry out its role in detoxification, and this leads to a buildup in chemicals such as ammonia within the blood. Gut bacteria are believed to be a prime source of these toxic substances. HE appears to result from the accumulation of these toxic substances, and is characterized by neuropsychological deficits that can range from impaired cognitive performance and anxiety, to disorientation and personality changes, to stupor and confusion, and finally to coma and death. One of the more classic signs of HE is asterixis, a flapping tremor of the hand. HE can be classified as minimal, episodic, or persistent. Overt HE is defined based on the severity of impairment in mental status and neuromotor functioning (i.e., asterixis).[3]

There are no data on the prevalence of cirrhosis in Canada, according to the Canadian Liver Foundation.[1] The manufacturer cites an estimated prevalence of cirrhosis in the US of approximately 800,000 to 1 million. Alcoholic liver disease and viral hepatitis are the most common conditions leading to cirrhosis. Overt HE is estimated to occur in 28% to 43% of patients with cirrhosis, and it is second only to ascites among the common complications of cirrhosis. HE is responsible for one-third to one-half of hospitalizations related to cirrhosis.[2]

1.2 Standards of Therapy

The most common approach to preventing overt HE has traditionally been the administration of lactulose. Lactulose is also the preferred treatment for overt HE. Lactulose is a disaccharide that is not absorbed, but instead stays in the gut and is metabolized by colonic flora to acidic compounds that alter the pH of the colon sufficiently to allow for greater ammonia excretion. Lactulose has been more commonly used as an osmotic laxative; therefore, the primary adverse effect is diarrhea. Lactulose has a short duration of action and therefore requires frequent administration, particularly as the patient's condition worsens. Another limitation is that it comes in a syrup form that has poor palatability for many patients.

Other approaches for preventing HE include use of antimicrobials such as metronidazole and neomycin for the purpose of reducing or eliminating the gut bacteria responsible for producing the toxins that cause HE. However, according to the clinical expert consulted by the CADTH Common Drug Review (CDR) on this review, these are not commonly used in Canada, and none are indicated for HE.

1.3 Drug

Rifaximin is an orally administered antibiotic, belonging to the rifamycin class of antibiotics (that includes rifampin). Its antibacterial actions are due to the inhibition of ribonucleic (RNA) polymerase, which inhibits RNA synthesis. It is a broad-spectrum antibiotic, with activity against gram-positive, gram-negative, aerobic, and anaerobic enterobacteria, and it is poorly absorbed (< 1%) from the gastrointestinal (GI) tract. The principal behind the use of rifaximin is elimination of the gut bacteria that are responsible for producing HE-causing toxins. Rifaximin is administered orally as a 550 mg tablet twice daily.

TABLE 2: KEY CHARACTERISTICS OF TREATMENTS FOR OVERT HE AVAILABLE IN CANADA

	RIFAXIMIN			LACTULOSE
Mechanism of Action	Antibiotic that stays within the gut. Kills bacteria that produce ammonia.			Not established, but appears to alter intestinal pH enough to increase conversion of ammonia to non-absorbable NH_4+. Other mechanisms of action, included altered bacterial gut flora, may also be responsible for efficacy.
Indication[a]	Prevention of episodes of overt HE.			Constipation
Route of Administration	Oral			Oral
Recommended Dose	550 mg twice daily			As needed
Serious Side Effects/ Safety Issues	Potential for resistance			Diarrhea

HE = hepatic encephalopathy.

The approved indication for rifaximin under review by the CDR and the requested listing criteria from the manufacturer are as follows:

Indication under review
For the reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥ 18 years of age.
Listing criteria requested by sponsor
For patients who are unable to achieve adequate disease control, i.e. controlling HE recurrence, with lactulose alone, or for patients who are at risk of recurrent HE who are unable to tolerate lactulose.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of rifaximin for reducing the risk of overt HE recurrence in patients ≥ 18 years of age.

2.2 Methods

Studies selected for inclusion in the systematic review included pivotal trials in support of the Health Canada indication for rifaximin, as well as those meeting the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with prior history of overt HE Subgroups: patients with inadequate control of HE while on lactulose at baseline; patients intolerant of lactulose at baseline
Intervention	Rifaximin 550 mg twice daily, alone or in combination with other drugs
Comparators	Lactulose Metronidazole Placebo
Outcomes	***Key efficacy outcomes:*** Mortality Overt HE episodes (including time to episode, proportion of patients with episode) HRQoL Hospitalization due to HE (including time to hospitalization, proportion of patients hospitalized) All-cause hospitalizations Bacterial peritonitis episodes (including time to episode, proportion of patients with episode) ***Other efficacy outcomes:*** Symptoms (mental status as measured by Conn score, neuromotor function as measured by asterixis grade) ***Harms outcomes:*** AEs SAEs WDAEs Notable harms (e.g., diarrhea, diarrhea due to *C. difficile*, infections, antimicrobial resistance)
Study Design	Published and unpublished RCTs

AE = adverse events; DB = double-blind; *C. difficile* = *Clostridium difficile;* HE = hepatic encephalopathy; HRQoL = health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Zaxine (rifaximin) and hepatic encephalopathy.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on September 9, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on January 21, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Databases (free), Internet Search and Open Access Journals. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4. Excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings From the Literature

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

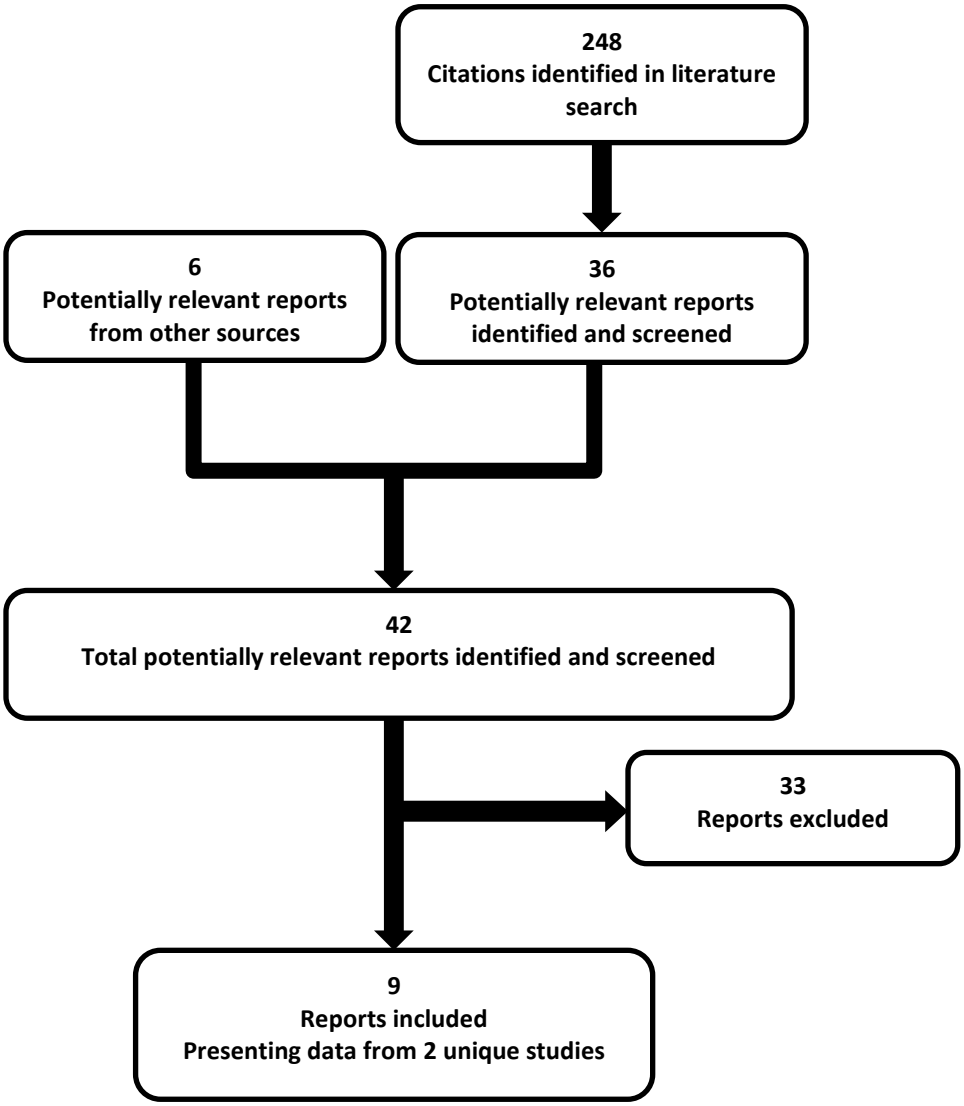

TABLE 4: DETAILS OF INCLUDED STUDIES

		Study 3001	Ali et al. (2014)
DESIGNS & POPULATIONS	**Study Design**	DB RCT, phase 3	DB RCT
	Locations	70 sites: Canada, US, Russia	1 site: Pakistan
	Study period	Dec 19, 2005 to Aug 15, 2008	Oct 2012 to Apr 2013
	Randomized (N)	299	126
	Inclusion Criteria	• Men and women ≥ 18 years of age • ≥ 2 episodes of HE associated with cirrhosis of the liver or portal hypertension, equivalent to Conn score ≥ 2 within 6 months before screening (i.e., recurrent HE) • In remission from HE (Conn score of 0 or 1) at the baseline assessment	• Men and women of any age • ≥ 2 episodes of HE in previous 6 months with Conn score ≥ 2 and a score of ≤ 25 on the MELD scale presenting as outpatients or admitted to ward • Patients admitted with HE precipitated by active, SBP, a potassium level of < 2.5 mmol/L, intercurrent infection, GI hemorrhage, constipation, or electrolyte imbalance due to diuretic use were enrolled only once these conditions were corrected.
	Exclusion Criteria	HE episodes primarily attributed to GI hemorrhage, medications (e.g., narcotics, tranquilizers, sedatives), renal failure requiring dialysis, or CNS insult were not considered to be prior HE episodes for the purposes of this study.	Known hypersensitivity to rifamycin and its metabolic products, a calcium level > 10 mg/dL, hepatocellular carcinoma, comorbidities such as chronic kidney disease, respiratory insufficiency, or cerebrovascular injury
DRUGS	**Intervention**	Rifaximin 550 mg tablets orally twice daily	Rifaximin 550 mg tablets orally twice daily
	Comparator(s)	Placebo (matching)	Placebo (matching)
DURATION	**Phase**		
	Run-in	1 week screening	NR
	DB	6 months	6 months
	Follow-up	2 week follow-up	NR
OUTCOMES	**Primary End Point**	Time to first breakthrough of overt HE episode defined as an increase of Conn score to ≥ 2 (i.e., from 0 or 1 to ≥ 2) or an increase in Conn score and asterixis grade of one grade each for those patients who entered the study with a Conn score of 0.	NR
	Other End Points	• Time to first HE-related hospitalization • Time to any increase from baseline in Conn score • Time to any increase from baseline in asterixis grade • Mean change from baseline in fatigue domain score on the CLDQ at EOT	NR

		Study 3001	Ali et al. (2014)
		• Mean change from baseline in venous ammonia concentration at EOT	
NOTES	**Publications**	Bass 2010;[7] Sanyal 2011[8]	Ali 2014[4]

CLDQ = Chronic Liver Disease Questionnaire; CNS = central nervous system; DB = double-blind; EOT = end of therapy; FDA = US Food and Drug Administration; GI = gastrointestinal; HE = hepatic encephalopathy; MELD = Model for End-stage Liver Disease; RCT = randomized controlled trial; SBP = spontaneous bacterial peritonitis.
Note: Four additional reports were included (Manufacturer's submission;[2] FDA Clinical Review;[9] FDA statistical review;[10] Health Canada Reviewers Report[11]).
Sources: Clinical Study Report for Study 3001[6] and Ali 2014.[4]

3.2 Included Studies

3.2.1 Description of studies

Two double-blind (DB), randomized controlled trials (RCTs) met the inclusion criteria for this review, both comparing rifaximin 550 mg twice daily to placebo. Study 3001 (N = 299) was a manufacturer-sponsored, multinational, phase 3 pivotal trial that enrolled patients who had had at least two episodes of overt HE within the six months before screening, and who were in remission from HE at baseline. Patients were randomized in an approximately 1:1 ratio to either rifaximin or placebo; the treatment period was six months in duration. Randomization was stratified by study site. The second included study, by Ali et al., was a published, single-centre trial conducted in Pakistan that compared rifaximin 550 mg twice daily to placebo over six months in patients who had had at least two episodes of overt HE episodes in the previous six months. This study does not appear to have been supported by the sponsor of the rifaximin submission to the CDR. Scant data were reported in the publication by Ali et al.; hence this review is focused primarily on Study 3001.

The primary outcome of Study 3001 was episodes of overt HE. Secondary outcomes included HE-related hospitalizations, time to increase in Conn score, time to improvement in asterixis grade, and mean change from baseline in the fatigue score on the Chronic Liver Disease Questionnaire (CLDQ). The study by Ali et al. did not identify a primary outcome.

3.2.2 Populations

a) Inclusion and exclusion criteria

Patients with at least two episodes of HE associated with cirrhosis of the liver or portal hypertension equivalent to Conn score of at least 2 in the six months before screening, and who were in remission from HE (Conn score of 0 or 1) at the time of the baseline assessment, were enrolled into Study 3001. Patients with episodes of HE that were primarily attributed to gastrointestinal (GI) hemorrhage, medications, renal failure requiring dialysis, or central nervous system (CNS) insult were not considered to have had prior HE episodes.

In the study by Ali et al., the inclusion criteria were similar to Study 3001; patients were required to have had at least two episodes of HE in the previous six months. Patients admitted with HE precipitated by active spontaneous bacterial peritonitis (SBP), a potassium level of < 2.5 mmol/L, or intercurrent infection, GI hemorrhage, constipation, or electrolyte imbalance due to diuretic use were enrolled only after these conditions had been corrected.

b) Baseline characteristics

Patients in Study 3001 were older (mean age of 56 years) than patients in the study by Ali et al. (mean age of 42 years); there were more male than female patients in Study 3001, but slightly fewer males than females in the study by Ali et al. In Study 3001, patients were predominantly White (86%), and most had had either two (70%) or three (22%) HE episodes in the previous six months. The most recent HE episode had been most commonly Grade 2 in severity on the Conn scale (82%), and the majority had been rated as Grade 0 (68%) or Grade 1 (28%) on the asterixis scale. On the Model End-stage Liver Disease (MELD) scale, most patients scored either ≤ 10 (27%) or 11 to 18 (63%). (The MELD score is used to estimate the three-month mortality risk for patients awaiting a liver transplant. Patients whose MELD score is between 10 and 19 have a 6% risk of death over the following three months, while patients with a score of 9 or less have a 2% risk.[12]) At baseline, 91% of patients had used lactulose.

With respect to differences in baseline characteristics between groups in Study 3001, there was a lower proportion of males in the rifaximin group (54%) versus the placebo group (67%). There were some small differences in the distribution of MELD scores, with fewer rifaximin patients than placebo patients (24% versus 30%) with scores of 10 or less, and more rifaximin patients than placebo patients (67% versus 60%) with scores of 11 to 18.

In the study by Ali et al., all patients had experienced at least two episodes of overt HE in the past (not just in the previous six months), but no data were reported on Conn scores or asterixis grades. The mean MELD score was 15.5 in the rifaximin group and 16.3 in the placebo group.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

	Study 3001		Ali et al. (2014)	
Title	RIFAXIMIN N = 140	PLACEBO N = 159	RIFAXIMIN N = 63	RIFAXIMIN N = 63
Mean (SD) age, years	55.5 (9.6)	56.8 (9.2)	42.9 (4.5)	40.2 (2.3)
Male, n (%)	75 (54)	107 (67)	31 (49)	29 (46)
Race, n (%)				
White	118 (84)	139 (87)	NR	NR
Asian	4 (3)	8 (5)	NR	NR
Black	7 (5)	5 (3)	NR	NR
Native Hawaiian/Pacific	2 (1)	1 (1)	NR	NR
American Indian/Alaskan Native	5 (4)	3 (2)	NR	NR
Other	3 (2)	3 (2)	NR	NR
Missing	1 (1)	0	NR	NR
Time since first HE diagnosis, mean (SD) months	20.8 (23.2)	21.9 (26.4)		
Number of HE episodes in past 6 months, n (%)				
2	97 (69)	111 (70)	Ever: 30 (48)	Ever: 25 (40)
3	29 (21)	35 (22)	33 (52)	38 (60)
4	5 (4)	8 (5)		
5	7 (5)	1 (1)		
≥ 6	2 (1)	3 (2)		
Past HE severity (Conn score at most recent episode before study), n (%)				
1	1 (1)	2 (1)	NR	NR

Title	Study 3001		Ali et al. (2014)	
	RIFAXIMIN N = 140	PLACEBO N = 159	RIFAXIMIN N = 63	RIFAXIMIN N = 63
2	115 (82)	130 (82)	NR	NR
3	20 (14)	24 (15)	NR	NR
4	3 (2)	2 (1)	NR	NR
Missing	1	1	NR	NR
Conn score at baseline, n (%)				
Gr 0	93 (66)	107 (67)	NR	NR
Gr 1	47 (34)	52 (33)	NR	NR
Asterixis grade at baseline, n (%)				
0	99 (69)	108 (68)	NR	NR
1	41 (29)	45 (28)	NR	NR
2	2 (1)	5 (3)	NR	NR
3	1 (1)	1 (1)	NR	NR
Mean MELD score at baseline	13.1 (3.6)	12.7 (3.9)	15.5 (3.5)	16.3 (2.9)
MELD score ≤ 10	34 (24)	48 (30)	NR	NR
11 to 18	94 (67)	96 (60)	NR	NR
19 to 24	12 (9)	14 (9)	NR	NR
≥ 25	0	0	NR	NR
Prior lactulose use, n (%)	128 (91)	145 (91)	NR	NR
Mean (SD) tablespoons lactulose	3.5 (3.2)	3.7 (2.5)	NR	NR
Mean (SD) stool count 2 days before screening	2.6 (1.7)	2.4 (1.5)	NR	NR

Gr = grade; HE = hepatic encephalopathy; MELD = Model for End-stage Liver Disease; NR = not reported; SD = standard deviation.
Source: Clinical Study Report for Study 3001.[6]

3.2.3 Interventions

In Study 3001, rifaximin was administered as a 550 mg tablet twice daily for six months. The placebo group was matched to the rifaximin group with respect to dosing regimen and appearance of study medication.

Lactulose was available throughout the study to patients who had been using lactulose at baseline. Dose modifications (i.e., reducing, increasing, stopping, and restarting lactulose therapy) were permitted as needed throughout the study for these patients. Lactulose was to be titrated to an appropriate dose according to accepted medical practice. Patients or caregivers were requested to contact the investigational site to discuss an increase in lactulose dose to counteract a perceived worsening of mental status, unless a lactulose dose increase was immediately needed for the safety of the patient. Patients not previously on lactulose were not to start lactulose unless the investigator believed there was an immediate need for this concomitant therapy.

In the study by Ali et al., rifaximin was administered as a 550 mg tablet twice daily for six months. The placebo group was matched to the rifaximin group with respect to dosing regimen and appearance of study medication. Rifaximin was obtained from Brooke's Pharmaceuticals (not Salix Pharmaceuticals,

the company that submitted rifaximin to CDR). Concomitant administration of lactulose was permitted in this study for all patients.

3.2.4 Outcomes

In Study 3001, the primary end point was the time to first breakthrough overt HE episode. A breakthrough overt HE episode was defined as an increase of Conn score to 2 or higher (i.e., from 0 or 1 to 2 or higher) or an increase in the Conn score and asterixis grade of one grade each for those patients who entered the study with a Conn score of 0. Time to breakthrough overt HE episode was defined as the duration from the time of the first dose of the study drug to the first breakthrough overt HE episode. Because patients were censored at the time of the breakthrough overt HE episode, the duration of HE episodes was not captured. Secondary outcomes included time to HE-related hospitalization, time to increase in Conn score, time to increase in asterixis grade, mean change from baseline in CLDQ-fatigue score, and mean change in venous ammonia concentrations.

The Conn score (West Haven Criteria) grading system is as follows:

- Conn score 0 = No personality or behavioural abnormality detected.
- Conn score 1 = Trivial lack of awareness, euphoria, or anxiety; shortened attention span; impairment of addition or subtraction.
- Conn score 2 = Lethargy; disorientation for time; obvious personality change; inappropriate behaviour.
- Conn score 3 = Somnolence to semi-stupor, responsive to stimuli; confused; gross disorientation; bizarre behaviour.
- Conn score 4 = Coma; unable to test mental state.

Further details regarding the validity of this instrument can be found in Appendix 5. No minimal clinically important difference (MCID) was identified for changes in Conn score.

The asterixis grading system is as follows:

- Grade 0 = No tremors
- Grade 1 = Rare flapping motions
- Grade 2 = Occasional, irregular flaps
- Grade 3 = Frequent flaps
- Grade 4 = Almost continuous flapping motions.

Further details regarding the validity of this instrument can be found in Appendix 5. No MCID was identified for changes in asterixis grade.

The Chronic Liver Disease Questionnaire (CLDQ) is the first disease-specific, health-related quality-of-life (HRQoL) instrument systematically developed to measure change over time in patients with chronic liver disease.[8,13] The CLDQ includes 29 items in the following six domains: fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry.[13] A seven-point scale is used for the response to each item; a score of 1 indicates the worst and a score of 7 indicates the best possible function.[13] Further details regarding the validity of this scale are provided in Appendix 5. It has been suggested that a change of 0.5 to 1 on the seven-point scale may represent a clinically significant difference; however, this does not appear to have been validated using conventional methods for estimating an MCID.

The study by Ali et al. did not identify a primary outcome. A breakthrough episode of HE was defined as a Conn score of 2 or higher precipitated by progression of disease, constipation, or electrolyte imbalance.

3.2.5 Statistical analysis

In Study 3001, the analysis of the primary efficacy end point was based on the comparison of time to first breakthrough overt HE episode between the rifaximin and placebo groups in the intention-to-treat (ITT) population, adjusting for analysis region (North America versus Russia), using the Cox proportional hazards model with a two-sided test at a significance level of 0.05. Additionally, Kaplan–Meier time-to-event methods were used to estimate the proportion of patients experiencing a breakthrough overt HE episode on days 28, 56, 84, 140, and 168 for each treatment group. Greenwood's formula for estimation of standard error (SE) was used to estimate SE at each time point. Kaplan–Meier results for each treatment group were illustrated in figures. Covariates, such as the MELD score, Conn score, asterixis grade, and duration of current verified remission at baseline were fitted in the model in case of imbalance at baseline for a clinically important variable.

Patients who completed the study and who did not experience a breakthrough overt HE event were censored at the time of their six-month visit. Patients who terminated early for reasons other than a breakthrough overt HE event (e.g., liver transplant, adverse event [AE], patient request) were contacted at six months from randomization to determine if they had experienced a breakthrough overt HE episode and to confirm vital status. Patients without a breakthrough overt HE event were censored at the time of contact or death, whichever was earlier. Therefore, complete capture was achieved for breakthrough overt HE episodes up to six months post-randomization.

Two sensitivity analyses were conducted. One sensitivity analysis excluded patients from the ITT population who had precipitating factors for overt HE (i.e., concomitant comorbid conditions such as azotemia; use of sedatives, tranquilizers, or analgesics; GI bleeding; excessive dietary protein intake; metabolic alkalosis; infection; constipation; or surgery, particularly transjugular intrahepatic portosystemic shunt [TIPS] procedures) at the time of randomization. The second sensitivity analysis excluded patients who took concomitant medications other than lactulose (e.g., neomycin) for the treatment or prevention of HE during the treatment phase.

The primary efficacy end point was analyzed for the following subgroups: sex (male versus female), age (< 65 years versus 65 years and older), race (White versus non-White), analysis region (North America versus Russia), baseline MELD level (≤ 10, 11 to 18, 19 to 24), baseline Conn score (0 versus 1), prior lactulose use (Yes versus No), diabetes at baseline (Yes versus No), duration of current verified remission (≤ 90 days versus > 90 days), and the number of HE episodes within the six months before randomization (2 episodes versus more than 2 episodes).

Key secondary end points were analyzed in a hierarchical fashion. Significance tests were conducted for all secondary efficacy end points. Results of significance testing were reported in a hierarchical order until a non-significant *P* value was found ($P > 0.05$). After finding a non-significant *P* value, all significance tests of subsequent end points were considered exploratory in nature. Time-to-event end points were analyzed as described for the primary efficacy end point. Mean changes from baseline in venous ammonia concentrations and in the CLDQ-fatigue domain score were analyzed using analysis of covariance (ANCOVA). Patients who discontinued early, before experiencing an HE-related hospitalization or an increase in Conn score or asterixis grade, were censored at the time of

discontinuation. For CLDQ, the last available post-baseline value was used for the calculation of mean change from baseline.

A total of 250 patients, approximately 125 each in the rifaximin and placebo groups, were planned for enrolment in the study. This sample size was based on a power calculation for the Cox regression analysis of time to first breakthrough overt HE episode. It was assumed that approximately 50% of rifaximin-treated patients and 70% of placebo-treated patients would experience a breakthrough overt HE event over the course of the six-month treatment period, resulting in a hazard ratio (HR) for rifaximin relative to placebo of approximately 0.58. Based on this assumption, sample size calculations showed that approximately 100 evaluable patients per treatment group would provide at least 80% power to demonstrate that rifaximin was superior to placebo. Approximately 125 patients per treatment group were randomized in order to compensate for the anticipated loss of patients due to liver transplant, GI bleeds, and other competing events.

Few details were provided regarding the statistical analysis plan in the study by Ali et al. Chi-square tests and t-tests were used to test for differences between groups for efficacy outcomes. No sample size calculation was reported, and there was no mention of controlling for multiple statistical testing.

3.2.5.1 Analysis populations

The study populations used in the analyses for Study 3001 were as follows:

- The ITT population, which included all randomized patients who received at least one dose of the study drug.
- The safety population, which included all randomized patients who received at least one dose of the study drug and who provided at least one post-baseline safety assessment.

No details were provided regarding the analysis populations in the Ali et al. study.

3.3 Patient Disposition

A large proportion of patients in each of the rifaximin and placebo groups discontinued Study 3001, with a much lower proportion of withdrawals in the rifaximin group versus the placebo group (37% versus 59% respectively). This was driven primarily by discontinuation due to HE breakthrough, the most common reason for withdrawal, which occurred in 20% of rifaximin patients and 43% of placebo patients.

Of 48 patients (24 in each group) who discontinued for reasons other than a breakthrough overt HE episode, 36 patients (17 and 19 in the rifaximin and placebo groups respectively) were contacted at six months post-randomization; of these, four patients in the rifaximin group and two patients in the placebo group had experienced breakthrough overt HE.

No details regarding disposition were provided in the Ali et al. study.

TABLE 6: PATIENT DISPOSITION: STUDY 3001

	Study 3001	
	RIFAXIMIN	**PLACEBO**
Screened, N	NR	
Randomized, N (%)	140	159
Discontinued, N (%)	52 (37)	93 (59)
HE breakthrough	28 (20)	69 (43)
AE	8 (6)	7 (4)
patient request	6 (4)	9 (6)
death	6 (4)	3 (2)
development of any exclusion criterion	1 (1)	3 (2)
liver transplant	0	1 (1)
other	3 (2)	1 (1)
Discontinued early due to non-breakthrough overt HE event and followed until 6 months post-randomization	17 (12)	19 (12)
ITT, N	140	159
PP, N	N/A	N/A
Safety, N	140	159

AE= adverse event; HE = hepatic encephalopathy; ITT = intention-to-treat; NR = not reported; PP = per-protocol.
Source: Clinical Study Report for Study 3001.[6]

3.4 Exposure to Study Treatments

In Study 3001, patients in the rifaximin group were exposed to therapy for a mean of 130 days; patients in the placebo group were exposed for a mean of 106 days. Treatment exposure was not reported by Ali et al.

In Study 3001, 91% of enrolled patients used lactulose during the treatment period: three patients receiving lactulose at baseline discontinued therapy during the trial, and another three patients not on lactulose at baseline started lactulose during the trial. Daily lactulose use was recorded by each patient in a diary. The mean daily lactulose dose was 3.1 tablespoons for the rifaximin group and 3.5 tablespoons for the placebo group. Lactulose use was not reported by Ali et al.

3.5 Critical Appraisal

3.5.1 Internal validity

The method of randomization in Study 3001 appears to have been appropriate for maintaining allocation concealment. Blinding was maintained by use of a matching placebo. There were no obvious differences in number of specific AEs, nor were there specific adverse events that were associated with use of rifaximin that might have allowed participants to guess their assigned treatment.

A high proportion of patients withdrew from Study 3001: 37% of patients in the rifaximin group and 59% of patients in the placebo group over the six-month course of the study. This is a potential concern with respect to the analysis of outcomes (e.g., quality of life) that use imputation methods such as last observation carried forward, as the integrity of randomization may be compromised and the sample remaining over time may be less reflective of the original, randomized population. The imbalance in withdrawal rates may also introduce bias in some outcomes (e.g., safety) due to differences in average follow-up, although the direction of any bias on safety outcomes would be unfavourable to the rifaximin group due to the lower withdrawal rates in this group.

The manufacturer employed a hierarchical testing procedure to account for multiple comparisons among secondary outcomes in Study 3001. Secondary outcomes were tested in order, and once a statistically non-significant ($P > 0.05$) result was obtained, subsequent analyses were considered to be exploratory. This meant that the comparison between treatment groups for hospitalization due to HE and improvement in Conn scores achieved statistical significance, while change in asterixis grade, the next outcome in the hierarchy, did not achieve statistical significance. Thus, subsequent testing of CLDQ-fatigue was exploratory in nature. It is not clear how outcomes were chosen for the hierarchical analysis and what the rationale was used for the ranking of outcomes within the hierarchy. As an example, quality of life was considered to be, based on clinical expert input, a key efficacy outcome for this review. However, it was only an exploratory outcome in the trialists' hierarchy of secondary outcomes.

According to the clinical expert consulted by CDR, the outcome of HE-related hospitalization may be somewhat subjective, as the threshold for deeming that a given patient requires hospitalization may vary across jurisdictions, institutions, and physicians, and may also be impacted by non-clinical patient factors such as the degree of social support. However, potential limitations to the objectivity of this outcome are unlikely to introduce bias in the relative probability of HE-related hospitalization for patients in the rifaximin versus placebo group in the context of a randomized, double-blind trial.

The Ali et al. study had numerous limitations with respect to methodology and reporting. There were very limited details provided with respect to study design, statistical analysis plan, and baseline characteristics. According to the manufacturer, there was no clinical study report available for this study, as it was conducted using rifaximin supplied by a local manufacturer in Pakistan. As such, the results of this study are difficult to interpret.

3.5.2 External validity

Lactulose represents the first-line therapy for the prevention and treatment of HE in Canada, and according to the clinical expert consulted by CDR, this is likely to continue despite the introduction of rifaximin. Hence, consistent with the listing criteria requested by the manufacturer, rifaximin is likely to be used for patients who are intolerant to lactulose or who have inadequate control and prevention of HE despite optimally tolerated doses of lactulose. However, the population enrolled in Study 3001 is not entirely reflective of the clinical population that will receive rifaximin. More than 90% of patients used lactulose at baseline and throughout the trial; therefore, the generalizability of trial results to lactulose-intolerant patients who will use rifaximin as monotherapy is uncertain. Furthermore, among the patients who used lactulose at baseline, it is uncertain to what extent attempts were made to optimize the dose of lactulose to maximize efficacy while maintaining an acceptable level of tolerability. Dosing of lactulose is typically titrated according to the number of daily stools, with a target of three per day. In the overall study population, the mean number of stools per day was reported as 2.5. Subgroup analysis by region showed that patients in the North American group may have been closer to being optimized to an average of three stools per day than patients in Russia (1.2 stools per day).

The six-month treatment period was likely of sufficient duration to assess the key efficacy outcome of overt HE episodes, judging from the large number of events in the study. However the chronic use of any antibiotic raises concerns about development of opportunistic infections and antimicrobial resistance. Study 3001 was likely not large enough or long enough to effectively assess these risks.

The Ali et al. study was conducted entirely at a single centre in Pakistan; hence, generalizability of the findings to Canada may be limited. The authors suggested, for example, that the gut flora of patients in that region of the world might differ significantly from the flora of patients living elsewhere. This might

impact the efficacy of rifaximin, which works by altering intestinal flora. Clinical practice patterns may also vary.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 3). See APPENDIX 4: DETAILED OUTCOME DATA *for detailed efficacy data.*

3.6.1 Hepatic encephalopathy breakthrough

Time to breakthrough overt HE was the primary outcome of Study 3001. There were 31 events of HE in the rifaximin group and 73 events in the placebo group at six months, for a HR of 0.421 (95% CI, 0.276 to 0.641, $P < 0.0001$) (Table 8).

In subgroup analyses, results were consistent for patients with significant comorbidities (HR 0.248 [95% CI, 0.108 to 0.571]) and without significant comorbidities (HR 0.512 [95% CI, 0.313 to 0.839]) that may increase the risk of developing overt HE. A subgroup analysis was also performed according to lactulose use at baseline (Table 12); however, there was only one event of overt HE in the rifaximin group and three events in the placebo group among the < 10% of patients who did not use lactulose at baseline. Due to the small event rate, the statistical non-significance of the effect estimate in this subgroup is inconclusive. The results of a sensitivity analysis excluding patients who received concomitant medications other than lactulose for the prevention or treatment of HE were consistent with the primary analysis (HR 0.419 [95% CI, 0.275 to 0.640]).

The manufacturer also reported Kaplan–Meier estimates at various time points (Table 7).

TABLE 7: KAPLAN–MEIER ESTIMATES OF OVERT HE OCCURRENCE AT VARIOUS TIME POINTS IN STUDY 3001

Time Point	Rifaximin (n/N)	Placebo (n/N)
Day 0 to < Day 28	13/140	20/158
Day 28 to < Day 56	4/126	23/137
Day 56 to < Day 84	6/120	14/113
Day 84 to < Day 140	7/112	10/98
Day 140 to < Day 168	1/98	6/84
Day 168 to trial end	0/46	0/38

HE = hepatic encephalopathy.

Ali et al. reported that there were 16 patients in the rifaximin group and 14 patients in the placebo group who had an overt HE episode (Table 9Table 9). There was no statistically significant difference between groups.

3.6.2 Mortality

In Study 3001, a similar percentage of patients in the rifaximin and placebo groups (7% in each group) died during the six-month study (Table 8). The most common cause of death with rifaximin was esophageal varices (three deaths in the rifaximin group, two deaths in the placebo group); the next most common reason was hepatic cirrhosis (0 patients in the rifaximin group and four patients in the placebo group). All-cause hospitalizations were not reported.

Seven patients died in each of the rifaximin and placebo groups in the Ali et al. study (Table 9Table 9). The authors noted that most of the deaths were related to either disease progression or infection.

3.6.3 Hospitalizations due to hepatic encephalopathy

There were 19 hospitalization events due to HE in the rifaximin group and 36 events in the placebo group (HR 500 [95% CI, 0.287 to 0.873], *P* = 0.0129) (Table 8).

Data for hospitalization due to HE was not reported in the Ali et al. study.

3.6.4 Health-related quality of life

Quality of life was assessed using the fatigue score on the Chronic Liver Disease Questionnaire (CLDQ) as a secondary end point, and the Short-Form 36-item Health Questionnaire (SF-36) as a tertiary end point. As a tertiary end point, no statistical analyses were planned for the SF-36. No formal analyses were performed for the CLDQ either, as the between-group difference in the previous outcome in the hierarchy, i.e., asterixis grades, was not statistically significant. Nevertheless, the difference between groups was reported as being not statistically significant (Table 8). Data for other domains of the CLDQ, including overall scores, were also provided by the manufacturer upon request; these were considered to be exploratory analyses. No statistically significant differences between the rifaximin and placebo groups were reported for any of these domains.

Quality-of-life data were not reported by Ali et al.

3.6.5 Bacterial peritonitis

Bacterial peritonitis was reported as an AE in Study 3001. After six months, 1% of rifaximin patients and 3% of placebo patients reported bacterial peritonitis as an AE (Table 8).

Bacterial peritonitis data were not reported by Ali et al.

3.6.6 Other efficacy outcomes

There were 37 events of worsened Conn scores in rifaximin patients and 77 such events in placebo patients (HR 0.463 [95% CI, 0.312 to 0.685], *P* < 0.0001) (Table 11).

There were 32 events of increased asterixis grades in the rifaximin group, and 50 such events in the placebo group (HR 0.646 [95% CI, 0.414 to 1.008], *P* = 0.0523) (Table 11).

TABLE 8: KEY EFFICACY OUTCOMES: STUDY 3001

	Study 3001	
	RIFAXIMIN N = 140	**PLACEBO N = 159**
Breakthrough Overt HE		
Events at 6 months	31	73
HR[a] [95% CI]	0.421 [0.276 to 0.641]	
P value[b]	< 0.0001	
No. of patients with HE event	NR	NR
Mortality		
N (%)	10 (7)	11 (7)
Most common causes:		
Hepatic cirrhosis	0	4
Esophageal varices	3	2
Hospitalizations, HE-related		

	Study 3001	
	RIFAXIMIN N = 140	**PLACEBO N = 159**
Events at 6 months	19	36
Time to event, HR [95% CI]	0.500 [0.287 to 0.873]	
P value	0.0129	
QoL: CLDQ		
Overall score		
Mean (SD) baseline	4.12 (1.16)	4.15 (1.17)
Mean (SD) change from baseline to EOT	0.12 (0.87) N = 96	0.06 (1.08) N = 106
P value	0.2426	
Fatigue		
Mean (SD) baseline	3.28 (1.33)	3.34 (1.41)
Mean (SD) change from baseline to EOT	0.30 (1.26) N = 95	0.11 (1.32) N = 105
P value[c]	0.9877	
Abdominal symptoms		
Mean (SD) baseline	4.61 (1.53)	4.58 (1.63)
Mean (SD) change from baseline to EOT	0.11 (1.40) N = 95	0.01(1.45) N = 105
P value	0.4434	
Systemic symptoms		
Mean (SD) baseline	4.50 (1.29)	4.56 (1.36)
Mean (SD) change from baseline to EOT	0.04 (1.08) N = 95	0.08 (1.16) N = 106
P value	0.6033	
Activity		
Mean (SD) baseline	4.13 (1.55)	4.08 (1.51)
Mean (SD) change from baseline to EOT	0.04 (1.51) N = 95	–0.08 (1.58) N = 105
P value	0.8222	
Emotional Function		
Mean (SD) baseline	4.44 (1.35)	4.43 (1.30)
Mean (SD) change from baseline to EOT	–0.02 (1.09) N = 95	0.08 (1.17) N = 106
P value	0.2420	
Worry		
Mean (SD) baseline	3.72 (1.74)	3.97 (1.54)
Mean (SD) change from baseline to EOT	0.26 (1.34) N = 95	0.10 (1.59) N = 106
P value	0.4081	
HRQoL: SF-36[d]		
Mean (SD) change from baseline to EOT: physical functioning[d]	0.28 (19.98) N = 118	–2.01 (22.81) N = 125
Mean (SD) change from baseline to EOT: Role physical	6.71 (50.23) N = 118	2.98 (18.0) N = 126
Mean (SD) change from baseline to EOT: Bodily pain	1.90 (21.90) N = 116	0.43 (27.4) N = 122
Mean (SD) change from baseline to EOT: General health	2.29 (18.88)	–2.40 (19.26)

	Study 3001	
	RIFAXIMIN N = 140	**PLACEBO N = 159**
	N = 117	N = 127
Mean (SD) change from baseline to EOT: Vitality	0.72 (10.92) N = 118	2.13 (14.83) N = 127
Mean (SD) change from baseline to EOT: Social functioning	2.01 (26.86) N = 118	0.10 (27.09) N = 126
Mean (SD) change from baseline to EOT: Role emotional	–3.95 (53.76) N = 118	6.88 (48.32) N = 126
Mean (SD) change from baseline to EOT: mental health	–1.88 (18.75) N = 118	–0.56 (18.91) N = 127
Episodes of Bacterial Peritonitis		
No. of patients reporting (as an AE), n (%)	2 (1)	4 (3)

CI = confidence interval; CLDQ = Chronic Liver Disease Questionnaire; EOT = end of therapy; HE = hepatic encephalopathy; HR = hazard ratio; NR = not reported; HRQoL = health-related quality of life; QoL = quality of life; SD = standard deviation.
[a] Time to first breakthrough overt HE episode was defined as an increase of Conn score to Grade 2 or higher (i.e., Grade 0 or 1 to 2 or higher) or an increase in Conn and asterixis grade of one grade each for those patients who entered the study with a Conn score of 0.
[b] HR estimates in the rifaximin group compared with the placebo group were determined from the Cox proportional hazards model with adjustment for region. *P* value was based on the Score statistic.
[c] Change from baseline in CLDQ-fatigue was a secondary outcome, but was based on hierarchical testing procedure; this was an exploratory analysis. All other CLDQ outcomes were exploratory.
[d] *P* values were not reported for Short-Form 36 Health Survey data.
Source: Clinical Study Report for Study 3001.[6]

TABLE 9: KEY EFFICACY OUTCOMES: STUDY BY ALI ET AL.

	Ali et al. (2014)	
Breakthrough HE	**RIFAXIMIN N = 63**	**PLACEBO N = 63**
Patients with ≥ 1 event	16	14
P value	0.203	
Mortality		
N (%)	7	7
P value	NR	
Hospitalizations, ALL		
N (%)	NR	NR
Hospitalizations, HE-related		
Events	NR	NR
Quality of life		
	NR	NR
Episodes of Bacterial Peritonitis		
	NR	NR

HE = hepatic encephalopathy; NR = not reported.
Source: Ali et al. (2014).[4]

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). *See* APPENDIX 4: DETAILED OUTCOME DATA *for* detailed *harms data.*

3.7.1 Adverse events

The proportion of patients with an AE was 80% in both treatment groups (Table 10). The most common AE was HE, reported in 12% of rifaximin patients and 21% of placebo patients. Other common AEs with a greater than 5% difference between the rifaximin and placebo groups were peripheral edema (15% versus 8%, respectively), and dizziness (13% versus 8% respectively).

AE event data were not reported by Ali et al. The authors noted that the incidence of AEs was similar between groups.

3.7.2 Serious adverse events

Serious adverse events (SAEs) were reported in 36% of rifaximin patients and in 40% of placebo patients (Table 10). The most common SAEs (rifaximin versus placebo respectively) were anemia (3% versus 0%), ascites (3% in each), esophageal varices (3% versus 1%), hepatic cirrhosis (2% versus 4%), pneumonia (3% versus 1%), and acute renal failure (1% versus 3%).

3.7.3 Withdrawal due to adverse events

There were 21% of rifaximin patients and 28% of placebo patients who withdrew due to an AE (Table 10Table 10). The most common reason for WDAE was HE (10% versus 19% in the rifaximin and placebo groups respectively).

3.7.4 Notable harms

Diarrhea was the most commonly occurring notable harm, occurring in 11% of rifaximin patients and in 13% of placebo patients (Table 10). Other notable harms that occurred in more than 1% of patients in either group (rifaximin versus placebo respectively) were bacterial peritonitis (1% versus 3%), and pneumonia (3% versus 1%). Diarrhea due to *Clostridium difficile* occurred in 1% of rifaximin patients and in none of the placebo patients.

TABLE 10: HARMS: STUDY 3001

	Study 3001	
AEs	**RIFAXIMIN N = 140**	**PLACEBO N = 159**
Patients with ≥ 1 AE, N (%)	112 (80)	127 (80)
Most common AEs		
HE	16 (12)	34 (21)
Peripheral edema	21 (15)	13 (8)
Dizziness	18 (13)	13 (8)
SAEs		
Patients with > 0 SAEs, N (%)	51 (36)	63 (40)
Most common SAEs		
Anemia	4 (3)	0
Ascites	4 (3)	4 (3)
Esophageal varices	4 (3)	2 (1)
Hepatic cirrhosis	3 (2)	6 (4)
Pneumonia	4 (3)	1 (1)
Acute renal failure	2 (1)	4 (3)
WDAEs		
WDAEs[a], N (%)	30 (21)	45 (28)
Most common reasons		
HE	14 (10)	30 (19)
NOTABLE HARMS		
Diarrhea	15 (11)	21 (13)
Bacterial peritonitis	2 (1)	4 (3)
Pneumonia	4 (3)	1 (1)
GI hemorrhage	1 (1)	3 (2)
Hematochezia	2 (1)	1 (1)
Bacteremia	1 (1)	2 (1)
Gastritis	2 (1)	0
C. difficile	2 (1)	0
Sepsis	0	2 (1)

AE = adverse event; *C. difficile* = *Clostridium difficile;* GI = gastrointestinal; HE = hepatic encephalopathy; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] WDAE includes patients who withdrew due to a serious HE adverse event.

Source: Clinical Study Report for Study 3001.[6]

4. DISCUSSION

4.1 Summary of Available Evidence

Two DB, RCTs met the inclusion criteria for this review, both comparing rifaximin 550 mg twice daily to placebo. Study 3001 (N = 299) was a six-month, manufacturer-sponsored, multinational phase 3 pivotal trial that enrolled patients who had had at least two episodes of overt HE within the six months before randomization, and who were in remission from HE at baseline. The second study, by Ali et al., was a published, single-centre trial conducted in Pakistan, and which does not appear to have been supported by the sponsor of the rifaximin submission to CDR. Minimal details regarding the design and results of that study were reported.

The primary outcome of Study 3001 was time to overt HE episode, and rifaximin was statistically significantly superior to placebo for this outcome (hazard ratio [HR] 0.421 [95% CI, 0.276 to 0.641], $P <$ 0.0001). Among key secondary efficacy outcomes in Study 3001, rifaximin was superior to placebo for hospitalizations related to HE (HR 0.500 [95% CI, 0.287 to 0.873]). Fewer rifaximin patients than placebo patients experienced an increase (worsening) in Conn scores, and this difference was statistically significant; however, there was no statistically significant difference between the rifaximin and placebo groups in the proportion of patients with worsening asterixis grades. Quality of life (QoL), measured by the fatigue score on the Chronic Liver Disease Questionnaire (CLDQ), was not significantly improved for rifaximin versus placebo, nor were there any apparent benefits measured by the Short-Form 36-item Health Questionnaire (SF-36). A similar proportion of patients died in the rifaximin and placebo groups (7% of patients in each group). Similar proportions of patients experienced adverse events (AES) between rifaximin and placebo (80% in each group). Diarrhea was the most common notable harm in each of the rifaximin and placebo groups (11% and 13% of patients respectively). Other notable harms that occurred in 1% to 3% of patients included bacterial peritonitis, pneumonia, and gastrointestinal (GI) hemorrhage. The study by Ali et al. reported no significant difference between the rifaximin and placebo groups in the proportion of patients who experienced overt HE.

4.2 Interpretation of Results

4.2.1 Efficacy

The requested listing criteria for rifaximin are for patients who are unable to achieve adequate disease control, i.e., prevention of HE recurrence with lactulose alone, or for patients who are at risk of recurrent HE and are unable to tolerate lactulose. This suggests that rifaximin is to be used either in combination with lactulose or as monotherapy for patients who are intolerant to lactulose. Most (91%) of the patients in Study 3001 were using lactulose at baseline and virtually all (99%) had had at least two episodes of HE within the previous six months, suggesting that they had failed to achieve adequate disease control while on lactulose. According to the clinical expert consulted by CDR, the dosing of lactulose in clinical practice for patients at risk of HE is a balancing act between achieving the desired level of control over HE symptoms and overt episodes and maintaining a tolerable level of laxation. The mean lactulose doses in Study 3001 were more than three tablespoons per day in both treatment groups; the expert consulted by CDR believed these to be reasonably reflective of the dosages used in clinical practice. As well, patients in North America had approximately three stools per day on average, suggesting that many of these individuals may have been receiving maximally tolerated doses of lactulose. However, it was uncertain to what extent lactulose dosing was optimized to maximize efficacy at baseline across the trial population, an aspect that potentially limits the generalizability of the results to patients considered for rifaximin therapy in clinical practice. Ideally, the efficacy and safety of rifaximin in this population should have been assessed through a trial in patients for whom optimized

lactulose did not achieve sufficient control of HE (e.g., occurrence of two overt HE episodes in the previous six months despite titration of lactulose to maximal tolerated doses).

Compared with patients with continuing occurrence of overt HE despite treatment with lactulose, patients who are "unable to tolerate" lactulose are less well defined. Lactulose can be poorly tolerated due to its laxative effect and low palatability. Therefore, a large number of patients could potentially fall under the "unable to tolerate" criteria. Unfortunately, no such population was clearly defined in Study 3001. Since more than 90% of patients used lactulose over the course of the trial, there are clearly difficulties in applying the results to patients who require rifaximin monotherapy due to lactulose intolerance.

The analysis of overt HE episodes in Study 3001 did not include an assessment of the severity or duration of episodes. Hence, it is unknown whether rifaximin impacts these parameters in addition to reducing the risk of overt HE. Rifaximin reduced the risk of HE-related hospitalizations compared with placebo; the HR was of a similar magnitude as for the primary outcome of overt HE episodes, suggesting that the reduction in hospitalization was likely driven by the lower risk of experiencing overt HE rather than reduced episode severity. The decision to hospitalize a patient may be influenced by factors such as capacity, availability of caregivers at home, and may also vary by region (i.e., North America versus Russia, the regions where Study 3001 was conducted), although blinding, randomization, and adjustment for region in the statistical models used to analyze trial results should have mitigated any confounding from these factors.

In their input to CDR, patients emphasized the negative impact that HE has on quality of life. Treatment with rifaximin versus placebo did not improve quality of life in the primary analysis on any of the CLDQ domains. The manufacturer attributed this lack of effect to the timing of the assessment, as it was not conducted during an overt HE episode, when quality of life is most severely impacted. According to the manufacturer, quality of life is difficult to assess during an HE event because patients are too impaired to accurately complete the survey. Conversely, a patient's quality of life would not be expected to differ substantially from baseline when assessed outside of an HE event. Sanyal et al. published a manufacturer-sponsored, post hoc, longitudinal re-analysis of CLDQ data from Study 3001 using time-weighted averages that found rifaximin significantly improved CLDQ scores compared with placebo.[8] However, the post hoc nature of this analysis, the lack of adjustments for multiple comparisons, and the uncertain clinical significance of the observed differences render these results difficult to interpret. One of the key quality-of-life issues related to preventing HE is the chronic use of lactulose, which causes diarrhea and other gastrointestinal symptoms and has an unpleasant taste. However, lactulose use was similar in the rifaximin and placebo groups; hence, it is unlikely to have contributed to the observed between-treatment quality-of-life effect estimates.

In addition to the pivotal phase 3 Study 3001, Ali et al. compared the approved dose of rifaximin 550 mg twice daily to placebo for the prevention of overt HE in a single-centre study in Pakistan. Although it was a small study, there was statistically significant improvement in risk of overt HE episodes with rifaximin versus placebo (i.e., the results were not consistent with Study 3001). The study authors hypothesized that the gut flora of their patients might have differed from those in the patients in Study 3001.[4] Practice patterns, such as the use of lactulose, could also differ between North America and Russia, the regions in which Study 3001 was conducted. Given the significant number of methodological and reporting issues associated with the study by Ali et al., the potential for bias is also high. Regardless of the reason, the apparent lack of benefit with rifaximin in the study by Ali et al. does little to detract from the positive efficacy results from Study 3001.

While rifaximin is indicated for reducing the risk of HE recurrence, input provided by the clinical expert consulted by CDR suggests that it may also be used to treat an overt HE episode. There may also be the potential for its use in patients experiencing minimal HE symptoms (e.g., "brain fog") despite the use of lactulose. Rifaximin has been available for some time outside Canada. There are a number of published studies of rifaximin for the management (both treatment and recurrence prevention) of HE at doses other than the 550 mg twice daily dose (total daily dose of 1,100 mg) approved in Canada, most commonly at a total daily dose of 1,200 mg. Two meta-analyses, both published in 2014, examined the effects of rifaximin on the management of HE.[14,15] Kimer et al. included 19 studies with 1,370 patients, with disaccharides as the most common comparator (eight trials), followed by placebo (six trials) and antibiotics (neomycin and paromycin, six trials). Trials were pooled regardless of the therapy used as control, although subgroup analyses were performed based on the type of therapy. For the treatment of HE, Kimer et al. found that rifaximin was more likely to achieve resolution of HE than the control group, with a relative risk (RR) of 1.34 [95% CI, 1.11 to 1.62]. There was no clear difference in effect sizes across different control therapies. Only one study was included for patients with minimal HE, and this trial reported a statistically significantly greater treatment effect versus placebo than the other trials. Kimer et al. also reported that rifaximin was associated with reduced mortality compared with the control [RR 0.64 (95% CI, 0.43 to 0.94)]. There was no indication of an increased risk of resistance to rifaximin or other antibiotics, nor was there an increased risk of *C. difficile*–associated enteritis. With respect to HE prevention, Kimer et al. included the same two trials captured in the current review.

The meta-analysis by Wu et al. focused on comparing rifaximin to non-absorbable disaccharides for the treatment of HE; eight RCTs were included, with a total of 407 patients. The authors defined clinical efficacy as an improvement in the HE syndrome, indicated by moving to a lower stage of HE or a significant decrease in the portosystemic encephalopathy index. Seven of the eight included studies reported on this outcome, and in the pooled analysis there was no statistically significant difference between rifaximin and the non-absorbable disaccharides (RR 1.06 [95% CI, 0.94 to 1.19], $P = 0.34$). Secondary outcomes of improvement in mental status and asterixis grade were also not statistically significantly different between rifaximin and non-absorbable disaccharides. With respect to harms, the authors focused on severe diarrhea and abdominal pain, finding a lower risk of diarrhea (RR 0.11 [95% CI, 0.04 to 0.31], $P < 0.0001$) and of abdominal pain (RR 0.19 [95% CI, 0.10 to 0.37], $P < 0.00001$) with rifaximin.

4.2.2 Harms

Diarrhea is one of the major drawbacks of using lactulose, and likely the prime reason why patients would be unable to tolerate this drug. However, most patients (> 90%) in Study 3001 were on lactulose during the study; a similar proportion of patients in the rifaximin and placebo groups reported diarrhea as an AE, suggesting that the addition of rifaximin may not cause further diarrhea. However, as might be expected, the mean dose of lactulose in the rifaximin group was slightly lower (3.1 tablespoons per day) than in the placebo group (3.5 tablespoons per day), which could have obscured rifaximin-induced diarrhea to a certain extent.

Given that rifaximin, an antibiotic, is intended for chronic use in HE prophylaxis, development of antimicrobial resistance and opportunistic infections are potential concerns despite the poor systemic bioavailability of this drug. Resistance is a potential concern not only for loss of efficacy with respect to the primary indication, HE prophylaxis, but also for the development of resistant organisms within the gut. In Study 3001, resistance did not appear to be an issue, although it was not clear what steps were taken to detect resistant organisms in the study. The risk of *C. difficile*–associated diarrhea was less than

1%. The sample size and six-month treatment period in this study were likely insufficient to assess the possible risk conferred by rifaximin with respect to opportunistic infections and resistance. A longer term, open-label extension trial of rifaximin is summarized in Appendix 6. With follow-up to at least 24 months, the proportion of patients with *C. difficile*–associated diarrhea remained less than 1%; hence, the risk did not appear to increase with extended treatment duration. Nevertheless, a warning about the risk of *C. difficile*–associated diarrhea appears in the Product Monograph for rifaximin. According to the manufacturer, resistance to rifaximin is not mediated by plasmids, which can be easily exchanged between organisms; therefore, the barrier to resistance may be higher than with other antibiotics used for HE prophylaxis. However, this hypothesis remains untested in patients at risk of HE.

4.3 Other Considerations

Rifaximin is a mild inducer of CYP3A4, but no clinically significant interactions involving CYP3A4 have been identified in healthy volunteers. However rifaximin is a *P*-glycoprotein (Pgp) substrate, and concomitant use of rifaximin with potent Pgp inhibitors might lead to increased levels of rifaximin.[5] The clinical significance of this effect is uncertain.

5. CONCLUSIONS

Two DB, RCTs met the inclusion criteria for this review, both comparing rifaximin 550 mg twice daily to placebo. Study 3001, a pivotal, manufacturer-sponsored, multi-centre phase 3 trial that enrolled 299 patients at risk of overt HE, provided the most reliable evidence and was the focus of the review. Rifaximin significantly reduced the risk of overt HE and HE-related hospitalization versus placebo in Study 3001. A similar proportion of patients died in the rifaximin and placebo groups. The effects of rifaximin on HRQoL were uncertain. Symptom scores in the rifaximin group were statistically significantly improved versus the placebo group on the Conn scale but not on the asterixis scale. There were no apparent differences in the incidence of adverse events (AEs) or SAEs between groups. The proportions of patients with diarrhea were similar in the rifaximin and placebo groups. Data from an open-label extension study at up to 24 months follow-up neither suggested new safety signals, nor an increased risk for previously observed AEs. There were insufficient data to determine the impact, if any, of rifaximin with respect to the risk of opportunistic infections or antimicrobial resistance. The risk of *C. difficile*–associated infections was low in both treatment groups in Study 3001, and did not appear to increase in the open-label extension study.

Lactulose dosing was not necessarily optimized for maximal efficacy and tolerability at baseline in Study 3001, and patients intolerant to lactulose were not specifically included. These aspects potentially limit the generalizability of the results of this study to Canadian clinical practice, as well as to the listing criteria requested by the manufacturer.

APPENDIX 1: PATIENT INPUT INFORMATION

This section was summarized by CADTH Common Drug Review staff based on the input provided by patient groups. It has not been systematically reviewed.

1. Brief Description of Patient Group(s) Supplying Input
Four organizations or patient groups provided patient input.

The Canadian Liver Foundation (CLF) supports liver disease research and public and professional education programs, patient support programs, and other fundraising and outreach efforts. The CLF has received unrestricted educational grants and/or has worked on joint initiatives with AbbVie Corporation, Astellas Pharma Canada Inc., Boehringer Ingelheim (Canada) Inc., Gilead Sciences Canada Inc., Janssen Inc., Merck Canada Inc., Novartis Pharmaceuticals Canada Inc., and Hoffmann-La Roche Limited. The CLF Chairperson has received honorariums from AbbVie Corporation, Boehringer Ingelheim (Canada) Inc., Merck Canada Inc., Janssen Inc., Hoffmann-La Roche Limited, Gilead Sciences Canada Inc., Vertex, and Bristol-Myers Squibb, and has contributed information to this submission.

The GI (Gastrointestinal) Society is committed to improving the lives of people with GI and liver conditions by supporting research, advocating for patient access in health care, and promoting GI and liver health. In the last two years, the GI Society has received funding from Abbott Laboratories Ltd., AbbVie Corporation, Amgen Canada Inc., Actavis (as Aptalis Pharma, Forest Laboratories, and Warner Chilcott), AstraZeneca Canada Inc., Bristol-Myers Squibb Canada, Rx&D (the association of Canada's research-based pharmaceutical companies), Ferring Inc., Gilead Sciences Canada Inc., GlaxoSmithKline Inc., Hoffmann-La Roche Ltd., Janssen Canada, Merck Canada Inc., Medical Futures Inc., Novartis Pharma Canada Inc., Cubist Pharmaceuticals (as Optimer Pharma), Pfizer Canada Inc., Sanofi-Aventis Canada Inc., Takeda Canada Inc., and Vertex Pharmaceuticals (Canada) Inc. It declared no conflict of interest in the preparation of this submission.

The Hepatitis C Education and Prevention Society (HepCBC) provides education, prevention and support to those living with hepatitis C (HCV) in British Columbia. HepCBC received funding, over the past three years, from Merck Pharmaceuticals, Hoffman-LaRoche, Vertex Pharmaceuticals, Gilead Sciences, Janssen Pharmaceuticals, Bristol-Myers Squibb, Boehringer Ingelheim, and AbbVie. The author has been funded by the pharmaceutical companies listed above for registration and travel to educational conferences and meetings.

The Consumer Advocare Network (Advocare) provides education and support to patient groups to promote engagement in health care policy and decision-making. It has received unrestricted educational grants to support education for hepatitis and related conditions from Janssen-Ortho, Roche, Merck, Vertex, and Wyatt Health Management. The author is a volunteer with Advocare; she is paid by the Canadian Organization for Rare Disorders and the Institute for Optimizing Health Outcomes, both of which also receive unrestricted funding from these entities for other programs. She declared no conflict of interest in relation to the preparation of this submission.

2. Condition and Current Therapy-Related Information
The submitting groups collected information from patients, caregivers, and health care professionals, including researchers, gastroenterologists, hematologists, and pharmacists from across Canada through surveys, interviews, and direct contacts.

All patient groups emphasized that hepatic encephalopathy (HE) is a common and very debilitating neuropsychiatric complication of liver disease. Characterized by a variety of symptoms affecting the patients' ability to think, function and move, HE can progress to coma and death. HE is classified into two primary forms: overt HE and minimal HE. A patient with overt HE exhibits clearly identifiable signs such as arm flapping (known as asterixis), stupor, seizures; overt HE can lead to coma and death. A patient with minimal HE (MHE) may have no overt or obvious symptoms of HE. MHE is diagnosed using sensitive neuropsychological and neurophysiological tests. Symptoms of HE have a significant impact on patients' quality of life and on their ability to function daily. Patients described the episodic nature of HE "attacks" which affect them physically and cognitively and often result in repeated and prolonged hospitalizations; the mental impact is like "walking around in a fog."

Patients with overt HE are often unable to perform major child care or other caregiver duties, and are often unable to work, thereby making them financially dependent upon caregivers and/or social assistance. This puts an extra burden on other family members who described the emotional toll associated with caring for HE patients. Additionally, patients with HE can experience personality changes and mood swings as well as confusion and memory loss that add to the caregivers' stress.

All submitting groups noted that lactulose is currently the first-line treatment for overt HE, but it causes significant side effects, including gas, bloating, abdominal pain, flatulence, and diarrhea. Due to necessary dosage adjustments, compliance can be a problem, leading to recurring episodes of HE when patients do not take their medication properly. In addition, not all patients respond to lactulose. Metronidazole, neomycin, and other antibiotics are sometimes tried.

3. Related Information About the Drug Being Reviewed

All patient groups reported that through the manufacturer's compassionate supply program and/or Health Canada's Special Access Program (SAP), some patients have been taking rifaximin alone or in combination with lactulose. Both HE patients and physicians reported a dramatic improvement with the use of rifaximin in terms of symptoms and reduced hospitalization. Although it is more expensive (per treatment) than lactulose, rifaximin is considered to be more cost-effective, as patients spend less time in hospital. Furthermore, patients report that rifaximin is easy to use (two pills per day), and it has minimal side effects. Patient groups noted that in terms of the patient's quality of life and for the caregivers, the advantages of rifaximin are significant. Rifaximin provides another treatment option, even if it does not completely eliminate the need for other medications or "stop HE" in either the short term or the long term.

Because Health Canada's SAP for rifaximin is no longer available due to Health Canada approval of rifaximin in August 2013, only patients with private insurance have coverage. Patient groups recognized that the cost factor would likely not make rifaximin the first drug to try, but to have it available (and financially accessible) is important for patients with HE.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 9, 2014
Alerts:	Weekly search updates until November 19, 2014
Study Types:	Randomized controlled trials; controlled clinical trials; multicenter studies; cohort studies; cross-over studies; case control studies; comparative studies; epidemiologic studies; also costs and cost analysis studies, quality of life studies, and economic literature.
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Line Strategy**
1	(zaxine or rifaximin* or Xifaxan or Xifaxanta or Rifamycin or Rifaxidin or Ritacol or Bang Yi or Colidimin or Coloximina or Faxinorm or Flonorm or Ifaxim or Lormyx or Normix or Qian Er Fen or Rifadom or Rifatime or Spiraxin or Targaxan or L 105SV or L105SV).ti,ab,ot,sh,hw,rn,nm.
2	(80621-81-4 or "80621814" or 806218 14 or "80621 0814" or UNII-L36O5T016N or UNIIL36O5T016N or 88747-56-2 or "88747562" or 88747 562 or 8874756 2).rn,nm.
3	1 or 2
4	3 use pmez
5	exp Hepatic Encephalopathy/
6	(Hepatic encephalop* or systemic encephalop* or portosystemic encephalop* or Hepatocerebral encephalop* or hepato cerebral encephalop* or hepatic coma* or hepatic stupor* or hepatic stupour* or Fulminant Hepatic Failure with Cerebral Edema* or coma hepaticum).ti,ab,ot,sh,hw.
7	5 or 6
8	7 use pmez
9	4 and 8
10	*rifaximin/
11	(zaxine or rifaximin* or Xifaxan or Xifaxanta or Rifamycin or Rifaxidin or Ritacol or Bang Yi or Colidimin or Coloximina or Faxinorm or Flonorm or Ifaxim or Lormyx or Normix or Qian Er Fen or Rifadom or Rifatime or Spiraxin or Targaxan or L 105SV or L105SV).ti,ab.
12	10 or 11
13	12 use oemezd
14	exp hepatic encephalopathy/
15	(Hepatic encephalop* or systemic encephalop* or portosystemic encephalop* or Hepatocerebral encephalop* or hepato cerebral encephalop* or hepatic coma* or hepatic stupor* or hepatic stupour* or Fulminant Hepatic Failure with Cerebral Edema* or coma hepaticum).ti,ab.
16	14 or 15
17	16 use oemezd
18	13 and 17
19	9 or 18
20	exp animals/
21	exp animal experimentation/ or exp animal experiment/
22	exp models animal/
23	nonhuman/
24	exp vertebrate/ or exp vertebrates/
25	animal.po.
26	or/20-25
27	exp humans/
28	exp human experimentation/ or exp human experiment/
29	human.po.
30	or/27-29
31	26 not 30

MULTI-DATABASE STRATEGY	
#	**Line Strategy**
32	19 not 31
33	32 not conference abstract.pt.
34	remove duplicates from 33

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	To July 11, 2014
Keywords:	Zaxine, rifaximin, Xifaxan, Xifaxanta, Rifamycin, L 105SV, HE, OHE, hepatic encephalopathy, hepatic encephalopathies
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
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APPENDIX 4: DETAILED OUTCOME DATA

TABLE 11: OTHER OUTCOMES: PHASE 3 STUDY

	Study 3001	
	RIFAXIMIN N = 140	**PLACEB0 N = 159**
Change in Conn Score		
Increase, events at 6 months	37	77
Time to event, HR [95% CI]	0.463 [0.312, 0.685]	
	P < 0.0001	
Change in Asterixis Grade		
Increase, events at 6 months	32	50
Time to event, HR [95% CI]	0.646 [0.414, 1.008]	
	P = 0.0523	

CI = confidence interval; CLDQ = Chronic Liver Disease Questionnaire; EOT = end of therapy; HE = hepatic encephalopathy; HR = hazard ratio; NR = not reported; QoL = quality of life; SD = standard deviation.
Source: Clinical Study Report of study 3001.[6]

TABLE 12: SUBGROUPS: PRIMARY OUTCOME

	Study 3001	
Time to Breakthrough HE Event[a]	**RIFAXIMIN N = 140**	**PLACEB0 N = 159**
Prior lactulose use: Yes		
Events	30 N = 128	70 N = 145
HR [95% CI]	0.418 (0.272 to 0.642)	
P value	*P* < 0.0001	
Prior lactulose use: No		
Events	1 N = 12	3 N = 14
HR [95% CI]	0.345 (0.036 to 3.324)	
P value	*P* = 0.3348	

CI = confidence interval; HE = hepatic encephalopathy; HR = hazard ratio.
[a] Time to first breakthrough overt HE episode was defined as an increase of Conn score to Grade 2 or higher (i.e., Grade 0 or 1 to 2 or higher) or an increase in Conn score and asterixis grade of one grade each for those patients who entered the study with a Conn score of 0.
[b] HR estimates in the rifaximin group compared with the placebo group was determined from the Cox proportional hazards model with adjustment for region. *P* value based on the score statistic.

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Objective

To summarize the validity of the following outcome measures reported in the included trials of rifaximin:

- Conn score
- Asterixis grade
- Chronic Liver Disease Questionnaire (CLDQ)

Findings

Conn score and asterixis grade are recommended by the US Food and Drug Administration (FDA) and are commonly used for grading the severity of hepatic encephalopathy (HE) in clinical and research settings. The Chronic Liver Disease Questionnaire (CLDQ) is a disease-specific, health-related quality-of-life (HRQoL) instrument systematically developed to measure longitudinal change over time in patients with chronic liver disease.

Conn Score

The Conn score, also known as the West Haven Criteria, is a 5-point scale (0 to 4) for grading the severity of HE based upon neurocognitive function (e.g., consciousness, intellectual function, and behaviour).[16-18] It was created by a working party at the 11th World Congress of Gastroenterology in Vienna, Austria in 1998.[19] Grade 0 represents a normal state or minimal HE (MHE); Grade 1, euphoria or anxiety; Grade 2, subtle personality change and inappropriate behaviour; Grade 3, somnolence and confusion; and Grade 4, coma (Table 1).[17,20-22] Clinically, patients with a Conn score of 2 or higher are diagnosed as having overt HE.[6,8,23] No evidence regarding the validity of the Conn score or the minimal clinically important difference (MCID) was identified. Although the Conn score has poor discrimination in low-grade HE, it has been widely used for assessment of HE severity in both clinical and research settings.[18-20]

TABLE 13: CLINICAL DESCRIPTIONS OF CONN SCORES

Conn Score	State Description
Grade 0	No apparent personality or behavioural abnormality
Grade 1	Trivial lack of awareness, euphoria or anxiety; shortened attention span; impairment of addition or subtraction
Grade 2	Lethargy; disorientation for time; obvious personality change; inappropriate behaviour
Grade 3	Somnolence to semi-stupor, responsive to stimuli; confused; gross disorientation; bizarre behaviour
Grade 4	Coma; unable to test mental state

Source: Briefing document for Gastrointestinal Drugs Advisory Committee.[17,24]

Asterixis Grade

Asterixis, also known as flapping tremor (i.e., flapping motions of the outstretched, dorsiflexed hands), is a commonly observed neuromotor symptom and a clinical sign of HE that increases in severity with the degree of neurological impairment. It occurs bilaterally in an asynchronous manner.[25] Asterixis is assessed with the patient holding both arms and forearms extended with wrists dorsiflexed and fingers open for 30 seconds.[26] The asterixis grading system (0 to 4) is presented in Table 14 below. The FDA recommended that asterixis be added as a component of symptom assessment in studies on HE[17] to provide a more sensitive and specific means of diagnosis and assessment of change, particularly at the

lower spectrum of the Conn scale (i.e., between 0 and 1), where discriminant power is poor.[17,25] No evidence was found of the validity or MCID of the asterixis grade.

TABLE 14: CLINICAL DESCRIPTION OF ASTERIXIS GRADES

Asterixis Grade	State Description
0	No tremors
1	Rare flapping motions
2	Occasional, irregular flaps
3	Frequent flaps
4	Almost continuous flapping motions

Source: Briefing document for Gastrointestinal Drugs Advisory Committee meeting.[17,25]

Chronic Liver Disease Questionnaire

The CLDQ is the first disease-specific HRQoL instrument systematically developed to measure change over time in patients with chronic liver disease. A comprehensive, methodological framework consistent with the development of other disease-specific HRQoL instruments was employed in developing the CLDQ.[8,13] It includes 29 items in the following six domains: fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry.[13] A seven-point scale is used to grade the response to each item; a score of 1 indicates the worst possible function and a score of 7 indicates the best possible function.[13] Each domain score is calculated by dividing the total of the scores for each item in the domain by the number of items in the domain.[13] Based on a survey (N = 60), patients found the CLDQ clear and easy to complete.[13] In another cross-sectional study (N = 133),[13] the CLDQ showed a gradient between patients without cirrhosis, Child's A cirrhosis, and those with Child's B or Child's C cirrhosis.[13] A direct association has been reported between the CLDQ and the EuroQol 5 Dimensions (EQ-5D) quality of life scale as well as the Short-Form 36-item Health Questionnaire (SF-36).[13,27] CLDQ has been widely validated and used.[13,27-31] The authors of the validation study concluded that CLDQ was short, easy to administer, produces both a summary score and domain scores, and correlates with the severity of liver disease.[13] Younossi et al.[32] reported that a change of 0.5 points on the scale from 1 to 7 would signify an important difference in score; however, there is no indication that this was validated using conventional methods for estimating MCID.[33]

Summary

The Conn score is a five-point scale (0 to 4) used to grade the severity of HE based upon neurocognitive function. A higher score indicates greater HE severity. Asterixis, also known as flapping tremor, is a clinical sign of HE. The asterixis grading system (0 to 4) is also a five-point scale, in which higher scores indicate more severe flapping tremor. The Conn score and asterixis grade are recommended by the FDA for studies of HE, and are commonly used for grading the severity of HE in clinical and research settings. However, no evidence on validity or MCID was identified for these outcomes. The CLDQ is a validated, widely used seven-point scale for assessing the HRQoL for patients with chronic liver disease. The CLDQ is correlated with the general HRQoL measures EQ-5D and SF-36. Higher scores indicate a higher quality of life. No evidence regarding MCID was identified.

APPENDIX 6: SUMMARY OF OPEN-LABEL MAINTENANCE TRIAL (STUDY 3002)

Objective

To summarize the findings of Study 3002,[34,35] an open-label extension study of rifaximin in patients with HE.

Findings

Study Characteristics

Study 3002[34,35] was a phase 3, 24-month, multi-centre, single arm, open-label maintenance (OLM) study of rifaximin in patients with hepatic encephalopathy (HE). The primary objective was to evaluate the long-term safety of rifaximin 550 mg twice daily. Patients included in the study came from two sources: 1) patients who participated in the previous pivotal randomized controlled trial (RCT) of rifaximin, Study 3001 (from 2005 to 2008);[6] 2) new patients enrolled from 2007 to 2010. The study enrolled adults (≥ 18 years) with a history of overt HE episodes (Conn score of 2 or higher) within the 12 months before screening and a Conn score of 2 or less at enrolment. Patients with a history of allergy to rifampin or rifaximin, severe medical conditions such as renal insufficiency, active tuberculosis, or current spontaneous bacterial peritonitis were excluded.

During the study, patients received oral rifaximin 550 mg twice daily for 24 months or more. Concomitant therapy with lactulose was optional. Safety was assessed for the "all-rifaximin" population (N = 392), which included all patients enrolled in the original RCT who had received rifaximin, regardless of whether they participated in Study 3002, as well as new patients who had not participated in the original RCT. The following subgroups were also defined:

- "New-rifaximin": patients (N = 252) who had not been previously treated with rifaximin because they were either in the placebo group of the original RCT or did not participate in the RCT.
- "Historical-rifaximin": patients (N = 140) who were in the rifaximin group of the original RCT, regardless of whether they participated in Study 3002.
- "Historical placebo": patients (N = 159) who were in the placebo group of the original RCT, regardless of whether they participated in Study 3002.

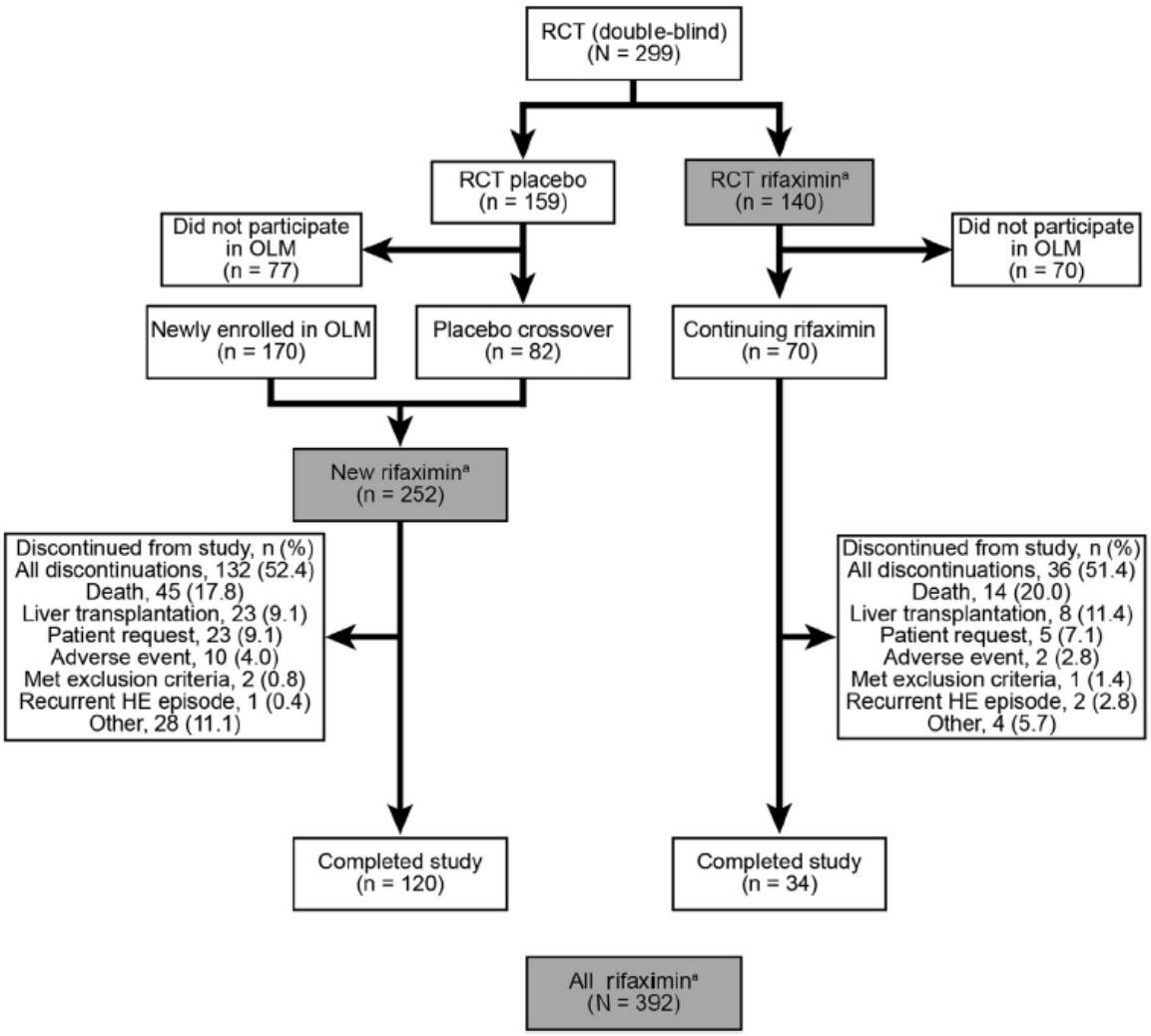
Outcomes assessed were mortality, hospitalization, and adverse events (AEs). Person-years of exposure (PYE) to rifaximin were calculated as follows: total exposure in days ÷ 365.25. AE rates were calculated as follows: number of patients with AE ÷ PYE, in which PYE reflected exposure until the AE occurrence and therefore may have differed from the PYE for the entire patient group. The rate of hospitalization events was calculated as follows: number of hospitalization events ÷ PYE, where PYE reflected exposure until the time the event occurred.

Overall, the inclusion and exclusion criteria and safety evaluations and definitions in Study 3002 were consistent with those in the pivotal RCT (Study 3001),[6-8] with the exception that Study 3002 enrolled patients with Conn scores of 2. The demographic and baseline characteristics of the historical placebo and rifaximin groups were similar to those of the Study 3002 population (Table 15).

Baseline Characteristics and Patient Disposition

Of the 392 patients in the all-rifaximin population, 83.7% (n = 328) were from either the US or Canada, and 16.3% (n = 64) were from Russia. Of the 392 patients, 70 patients were treated with rifaximin in the original RCT but did not participate in Study 3002, leaving 322 patients who were enrolled in the OLM. Of these, 170 were new patients who had not participated in the original RCT. Patient flow from the original RCT to the OLM and reasons for OLM discontinuation are shown in FIGURE 2.

FIGURE 2: CONSORT FLOW DIAGRAM



CONSORT = Consolidated Standards of Reporting Trials; HE = hepatic encephalopathy; OLM = open-label maintenance (trial); RCT = randomized controlled trial.

[a] The integrated safety population (all-rifaximin population, N = 392) included the new-rifaximin population plus all patients who received rifaximin during the RCT regardless of enrolment into the OLM trial (grey shaded boxes). Source: Manufacturer's submission.[2]

Demographic characteristics, liver disease history, and HE severity (baseline Conn score and asterixis grade) were similar among the all-rifaximin, new-rifaximin, historical-rifaximin, and historical placebo groups (Table 15). With regard to the historical placebo and rifaximin populations, 69.8% and 69.3% of patients respectively, had a history of two HE episodes in the previous six months, with the remaining patients having had more than two HE episodes. With regard to the new-rifaximin population, 71.4% of patients had had two or more HE episodes in the previous 12 months before Study 3002.

The median exposure to rifaximin was 427.0 days (range, 2 days to 1,427 days; PYE, 510.5) for the all-rifaximin population and 475.5 days (range, 2 days to 1,147 days; PYE, 342.3) for the new-rifaximin population. Among the 392 patients in the all-rifaximin population, 352 (89.8%) received concomitant lactulose (range, 15 mL per day to 300 mL per day), and 40 (10.2%) received rifaximin alone.

TABLE 15: BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS

Characteristic	Historical Placebo Population (N = 159)	Historical-rifaximin Population (N = 140)	New-rifaximin Population (N = 252)	All-rifaximin Population (N = 392)
Age, yrs, mean (SD)	56.8 (9.18)	55.5 (9.57) *P* = 0.22	57.5 (8.93) *P* = 0.47	56.8 (9.21) *P* = 0.95
< 65 yrs	128 (80.50)	113 (80.71) *P* = 1.0	197 (78.17) *P* = 0.62	310 (79.08) *P* = 0.82
Sex, n (%)				
Male	107 (67.30)	75 (53.57) *P* = 0.02	158 (62.70) *P* = 0.40	233 (59.44) *P* = 0.10
Female	52 (32.70)	65 (46.43)	94 (37.30)	159 (40.56)
Race, n (%)				
White	139 (87.42)	118 (84.29)	233 (92.46)	351 (89.54)
Black	5 (3.14)	7 (5.00) *P* = 0.51	10 (3.97) *P* = 0.12	17 (4.34) *P* = 0.46
Other/missing	15 (9.43)	15 (10.71)	9 (3.57)	24 (6.12)
Duration of current remission, d, mean (SD)	73.1 (51.33)	68.8 (47.68) *P* = 0.45	111.1 (108.63) *P* <.0001	95.9 (93.73) *P* = 0.04
Time since diagnosis of liver disease, mo, mean (SD)	60.51 (64.89)	51.22 (49.17) *P* = 0.17	74.91 (83.49) *P* = 0.07	66.45 (73.92) *P* = 0.38
Time since diagnosis of HE, mo, mean (SD)	21.85 (26.41)	20.84 (23.13) *P* = 0.73	20.02 (25.26) *P* = 0.48	20.31 (24.50) *P* = 0.52
MELD score, mean (SD)	12.7 (3.94)	13.1 (3.64) *P* = 0.39	12.6 (4.11) *P* = 0.82	12.8 (3.95) *P* = 0.84
MELD score category, n (%)				
≤ 10	48 (30.19)	34 (24.29)	88 (34.92)	122 (31.12)
11 to 18	96 (60.38)	94 (67.14) *P* = 0.45	137 (54.37) *P* = 0.74	231 (58.93) *P* = 0.53
19 to 24	14 (8.81)	12 (8.57)	23 (9.13)	35 (8.93)
Conn score, n (%)				
0	107 (67.30)	93 (66.43)	157 (62.30)	250 (63.78)
1	52 (32.70)	47 (33.57) *P* = 0.90	83 (32.94) *P* = 0.34	130 (33.16) *P* = 0.49

Characteristic	Historical Placebo Population (N = 159)	Historical-rifaximin Population (N = 140)	New-rifaximin Population (N = 252)	All-rifaximin Population (N = 392)
≥ 2	0	0	12 (4.76)	12 (3.06)
Asterixis grade, n (%)				
0	108 (67.92)	96 (68.57)	172 (68.25)	268 (68.37)
1	45 (28.30)	41 (29.29) *P* = 1.0	64 (25.40) *P* = 1.0d	105 (26.79) *P* = 0.92d
≥ 2	6 (3.77)	3 (2.14)	16 (6.35)	19 (4.85)
Renal impairment (serum creatinine), n (%)				
≥ 1.5 ULN	3 (1.89)	4 (2.86)	5 (1.98)	9 (2.30)
≤ 1.5 ULN	156 (98.11)	136 (97.14) *P* = 0.71	245 (97.22) *P* = 1.0	381 (97.19) *P* = 1.0

d = days; MELD = Model for End-Stage Liver Disease; mo = months; SD = standard deviation; ULN = upper limit of normal; yrs = years.
Note: *P* values are for rifaximin versus historical placebo.

Results

Mortality: Seventy-six deaths were reported in the all-rifaximin population, the majority of which were due to liver disease complications (56.6%); 19.7% were attributed to cardiac causes, and 10.5% were due to infection (pneumonia or sepsis). No deaths were attributed to the rifaximin treatment. The mortality rate (0.15 deaths/PYE) was similar to the rate reported for the historical placebo group (0.24 deaths/PYE), and causes of death in the OLM trial were consistent with those in the RCT phase.

All-cause and HE-related hospitalizations: In the all-rifaximin group, 109 HE-related hospitalizations were reported (0.21 events/PYE); 70 such hospitalizations were reported in the new-rifaximin group (0.23 events/PYE). These rates were similar to the rate observed in the historical-rifaximin group (0.30 events/PYE) and were lower than the rate observed in the historical placebo group (0.72 events/PYE). Similarly, the rates of all-cause hospitalizations were lower during treatment with OLM rifaximin compared with the historical placebo group (0.44 versus 1.30) in the OLM rifaximin and historical placebo groups respectively.

Adverse events: Event rates for total AEs, cirrhosis complications, and gastrointestinal AEs are summarized in Table 16, Table 17, and Table 18. It was found that AE rates in the all-rifaximin group were lower than in the historical-rifaximin and historical placebo groups. Similarly, the event rate for serious AEs in all-rifaximin patients (0.48) was lower than in the historical placebo group (1.37). The results for the new-rifaximin population were similar to those for the all-rifaximin population.

TABLE 16: SUMMARY OF ADVERSE EVENTS

	Historical Placebo Population (n = 159)[a]	Historical-rifaximin Population (n = 140)[a]	New-rifaximin Population (n = 252)	All-rifaximin Population (N = 392)
PYE	46.0	50.0	342.3	510.5
AEs: number of patients (rate[b])				
Any AE	127 (2.76)	112 (2.24)	236 (0.69)	362 (0.71)
Any SAE	63 (1.37)	51 (1.02)	158 (0.46)	244 (0.48)
WDAE	45 (0.98)	30 (0.60)	77 (0.22)	130 (0.25)

AE = adverse event; PBO = placebo; PYE = person-years of exposure; SAE = serious adverse event; WDAE = withdraw due to adverse event.

[a] Primary results were extracted from the pivotal study.[23]

[b] AE rates were calculated as follows (number of patients ÷ PYE), in which PYE reflected the exposure until the AE occurrence and therefore may have differed from the PYE for the entire patient group.

With respect to cirrhosis complications, infection event rates per PYE for all-rifaximin patients (0.73) were lower than those observed in the historical-rifaximin (1.12) and historical placebo groups (1.33) (Table 17). The use of antibiotics did not generally increase over the course of the OLM period. Six rifaximin-treated patients (two in the RCT and four in the OLM) had *C. difficile* infections (event rate, 0.012/PYE); the rates of *C. difficile* occurrence remained stable over the course of the OLM period (Table 17). All six patients had multiple risk factors for *C. difficile* infection. The rates for other complications of cirrhosis, including ascites and edema, variceal bleeding, anemia, and prolongation of coagulation tests, did not change significantly with long-term use of rifaximin and appeared similar to the rates noted in the historical placebo group. The incidence of gastrointestinal (GI)-related AEs, including the incidences of nausea and abdominal pain, was higher in patients treated with rifaximin plus lactulose compared with those treated with rifaximin alone (69.6% versus 47.5% respectively; $P < 0.001$) (Table 18).

TABLE 17: COMPLICATIONS OF CIRRHOSIS

	Historical Placebo Population (n = 159)	Historical-rifaximin Population (n = 140)	All-rifaximin Population (N = 392)
PYE	46.0	50.0	510.5
Infections (all), n (rate)	49 (1.33)	46 (1.12)	214 (0.73)
Infections of special interest			
Cellulitis	3 (0.07)	3 (0.06)	34 (0.07)
C. difficile	0	2 (0.04)	6 (0.01)
Peritonitis	6 (0.13)	3 (0.06)	22 (0.04)
Pneumonia	1 (0.02)	4 (0.08)	42 (0.08)
Sepsis/septic shock	5 (0.11)	2 (0.04)	31 (0.06)
Urinary tract/kidney	14 (0.32)	9 (0.19)	83 (0.19)
Complications of portal hypertension, n (rate)	37 (0.89)	40 (0.96)	195 (0.57)
Acute kidney injury/hepatorenal syndrome	9 (0.20)	2 (0.04)	74 (0.15)
Ascites and edema	29 (0.69)	34 (0.81)	147 (0.39)
Varices and variceal/GI bleed	7 (0.15)	6 (0.12)	58 (0.12)
Hematologic complications, n (rate)	7 (0.16)	13 (0.27)	80 (0.18)
Anemia	6 (0.13)	11 (0.23)	65 (0.14)
Thrombocytopenia/coagulation	1 (0.02)	3 (0.06)	33 (0.07)
Other, n (rate)			
Electrolyte imbalances	3 (0.07)	6 (0.12)	52 (0.11)
Fatigue/sleep disorders	29 (0.70)	26 (0.58)	93 (0.2)
Muscular atrophy	2 (0.04)	0	8 (0.02)

GI = gastrointestinal; PYE = person-years of exposure.

TABLE 18: GASTROINTESTINAL EVENT RATES FOR PATIENTS TREATED WITH RIFAXIMIN WITH OR WITHOUT LACTULOSE (REPORTED IN AT LEAST 5% OF PATIENTS IN EITHER GROUP)

	Rifaximin Alone (n = 40)	Rifaximin + Lactulose (n = 352)
PYE	57.6	452.9
GI disorders, % of patients (rate)		
Overall	47.5 (0.51)	69.6 (1.19)
Abdominal pain	12.5 (0.09)	21.3 (0.20)
Ascites	12.5 (0.09)	17.6 (0.15)
GI bleeding event	10.0 (0.08)	15.9 (0.14)
Nausea	7.5 (0.05)	24.1 (0.23)
Constipation	7.5 (0.06)	12.2 (0.11)
Vomiting	5.0 (0.04)	15.1 (0.13)
Diarrhea	5.0 (0.04)	13.6 (0.12)
Esophageal varices	5.0 (0.04)	5.7 (0.05)
Diverticulum	5.0 (0.04)	1.1 (0.01)
Abdominal distension	2.5 (0.02)	6.3 (0.05)

GI = gastrointestinal; PYE = person-years of exposure.

Limitations

Although the design of Study 3002 was aligned with regulatory guidance and published recommendations,[36,37] and despite the apparent similarity across groups with respect to demographic and baseline characteristics, there is the potential for confounding when comparing the new-rifaximin or all-rifaximin groups with the historical-rifaximin or historical placebo groups.

Summary

Based on the results of Study 3002, reductions in the rate of HE-related and all-cause hospitalization appear to be maintained with long-term treatment (24 months or longer) with rifaximin (550 mg, twice daily). The rates and types of AEs with long-term rifaximin treatment were similar to those observed in the original RCT.

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