NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Rifaximin-α (TARGAXAN® 550)

Norgine Pharmaceuticals Ltd

Single technology appraisal (STA)

Specification for manufacturer/sponsor submission of evidence

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Abbreviations

AE	Adverse event
BID	Twice daily
CFF	Critical flicker frequency
CRF	Case report form
CLDQ	Chronic Liver Disease Questionnaire
ESS	Epworth Sleepiness Scale
GI	Gastrointestinal
HE	Hepatic encephalopathy
HR	Hazard Ratio
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
MELD score	Model End Stage Liver Disease score
NHS	National Health Service
QALY(s)	Quality adjusted life year(s)
QoL	Quality of life
RCT	Randomised controlled trial
SAE	Serious adverse event
SBP	Spontaneous bacterial peritonitis
SF-36	Short-form 36
SPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event
TIPS	Transjugular intrahepatic portosystemic shunt

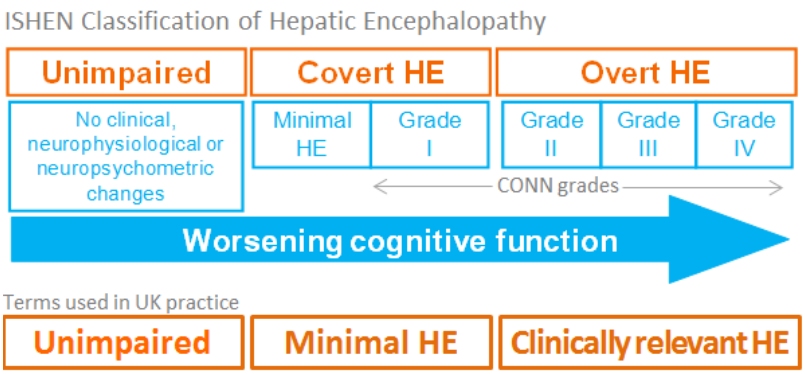
Executive summary

Hepatic encephalopathy (HE) is a reversible neuropsychiatric disorder caused by accumulation in the bloodstream of toxins that are normally removed by the liver. HE encompasses a spectrum of neuropsychiatric abnormalities seen in patients with established liver disease, and is most commonly associated with liver cirrhosis (1, 2). Patients with HE may experience symptoms ranging from subtle neurological abnormalities (e.g. mood alterations, changes in reaction times in daily activities such as driving), to severe neurological impairment (e.g. difficulty in moving and communicating) and in extreme cases, coma (2-4).

HE is commonly defined based on severity (see Figure 1).

The severity of HE is characterised by clinical symptoms of mental deterioration using Conn grade[1] in which higher scores indicate a higher severity. The ISHEN (International Society for Hepatic Encephalopathy and Nitrogen Metabolism) classification terms patients as either unimpaired, covert (Conn grade 0 or 1) or overt (Conn grade 2, 3 or 4) (16).

Figure 1: ISHEN classification of hepatic encephalopathy



CONN (West Haven) Criteria for the grading of mental state in Hepatic Encephalopathy

Grade	Description
0	No abnormalities detected
I	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impaired performance of addition
II	Lethargy or apathy Minimal disorientation for time or place Subtle personality change Inappropriate behaviour Impaired performance of subtraction
III	Somnolence to semi-stupor, but responsive to verbal stimuli Confusion Gross disorientation
IV	Coma (unresponsive to verbal or noxious stimuli)

To put this into UK context (Figure 1), UK liver specialists[2] noted that in UK clinical practice the terms covert and overt are not commonly used. Patients are often referred to as having "minimal HE/remission" (covert) or episodes of "clinically relevant HE"

[1] Hepatic encephalopathy can be graded using the Conn grade (also called the West Haven classification) in which higher scores indicate a higher severity, Grade 0-4 where Grade 0 represents: no personality or behavioural abnormality detected – Grade 4: coma (unresponsive to verbal or noxious stimuli). Note Conn grade and Conn score are used interchangeably throughout the document

[2] An advisory board with 9 with liver specialists in the UK and subsequent individual interviews were conducted to inform this submission with regard to the clinical pathway, validation and estimation of model parameters (in the absence of published/trial evidence). Termed 'expert opinion' from this point onwards in the document

(overt).[3] After an overt episode, patients usually return to an unimpaired or minimal HE state and this is considered to constitute a state of remission.

HE is associated with diminished health related quality of life (HRQoL) across both physical and mental domains (5-10) and represents a substantial burden on carers (4, 11).

The seriousness of HE is emphasised by the strong association between mortality and a history of overt HE episodes. In a study of patients with liver cirrhosis and a history of recurrent, overt HE episodes, survival rates were 42% at 1 year, and 23% at 3 years after experiencing an HE episode (12). In another analysis, the occurrence of a HE episode of Conn score 2 in patients with cirrhosis was associated with a 4-fold increase in the risk of death (13). A recent audit of 100 patients with cirrhosis admitted to a liver Intensive Care Unit (ICU) where HE was the primary indication for admission (59% Grade 3; 41% Grade 4) reported 30 days survival at 46% and 28% for patients with Grade 3 and Grade 4 HE, respectively (14).

No specific information on life expectancy of patients with recurrent episodes of HE in England and Wales could be found.

The number of patients with recurrent episodes of HE in England and Wales is uncertain. Based on a crude calculation it is estimated that 23,606 people in England and Wales with cirrhosis may have subclinical or mild HE and approximately 23%-40% of these (5,429-9,442) may progress to the most severe form of disease (15-17). We anticipate that that the maximum number of patients eligible for treatment annually would be approximately 9,442.

Whilst a patient is in remission or experiencing minimal HE symptoms they may be managed effectively at home independently or by their family or carer. However, if a patient experiences an acute overt or clinically relevant episode they are usually admitted to hospital for active management and treatment. According to UK clinicians, approximately 80% of patients admitted to hospital have grade 2 or grade 3 HE, with grade 2 representing the most common presentation. Some patients suffering from a severe HE episode will also require admission to an Intensive Care Unit.

Recurrent HE episodes are a distressing aspect of chronic liver disease for both patients and their carers, that entail considerable use of NHS resources in the form of hospitalisations, and may be associated with a poorer prognosis for the patient in terms of increased mortality (12, 14, 18-20). Reduction in recurrence of episodes of overt HE is therefore an important treatment goal for patients with liver cirrhosis. There are currently

[3] Throughout the document the terms ‘covert’ ‘minimal HE/remission’ are used interchangeably dependent on the source of the information. Similarly ‘overt’ and ‘clinically relevant HE’ are used interchangeably dependent on the source of the information.

no other UK or European licensed treatments for the reduction in recurrence of episodes of overt HE.

Whilst lactulose is not licensed for the reduction in recurrence of episodes of overt HE, it is the current standard of care and is the most routinely used therapeutic option for patients with ongoing HE at this time.

Norgine does not consider neomycin or neomycin with lactulose to be valid comparators, and requested for neomycin to be removed from the final scope for this appraisal. Additionally, a number of UK liver specialists are also in agreement that neomycin is not routinely used in the prevention of recurrent episodes of HE. Furthermore, neomycin is not licensed for the prevention of recurrence of overt HE episodes and the summary of product characteristics (SPC) carries a number of warnings relating to hepatic impairment and to long-term use. Consequently, Norgine believe that neomycin is inappropriate as a comparator for long-term treatment and the prevention of HE recurrences (21).

Rifaximin is a non-absorbed antibacterial drug of the rifamycin class that irreversibly binds the beta sub-unit of the bacterial enzyme DNA-dependent RNA polymerase, and consequently inhibits bacterial RNA synthesis. It has a broad antimicrobial spectrum against most of the Gram-positive and Gram-negative, aerobic and anaerobic bacteria, including ammonia producing species. Rifaximin may inhibit the division of urea-deaminating bacteria, thereby reducing the production of ammonia and other compounds that are believed to be important to the pathogenesis of HE.

Rifaximin is indicated for the reduction in recurrence of episodes of overt HE in patients ≥ 18 years of age and as such is the first and only licensed pharmacological treatment for this indication. The recommended daily dose is 1100 mg per day (one 550 mg tablet taken orally, twice a day). The rifaximin NHS list price is £259.23 for a 56 tablet pack.

Rifaximin is the only treatment that has demonstrated a reduction in the recurrence of episodes of overt HE, and hospitalisation due to HE, compared to placebo in a 6 month randomised, double blind, placebo-controlled study (~91% patients were taking concomitant lactulose in both arms). Patients who were in remission from HE, resulting from chronic liver disease, demonstrated that:

- Rifaximin 550 mg BID plus lactulose significantly reduced ($p<0.001$) the relative risk of recurrence of overt HE episodes by 58% (Hazard ratio 0.42) vs. placebo plus lactulose over 6 months (22).

- Rifaximin 550 mg BID plus lactulose significantly reduced ($p=0.01$) the relative risk of hospitalisation involving HE by 50% (Hazard ratio 0.50) vs. placebo plus lactulose over 6 months (22).

- The incidence of adverse events reported during the study was similar between the rifaximin and placebo groups, as was the incidence of serious adverse events.

- Additionally, it has been shown that long term treatment over 24 months with rifaximin 550 mg BID plus lactulose afforded continued protection from HE, reduced the hospitalisation rate, and did not adversely affect safety or mortality in patients with cirrhosis (23).

An economic analysis was undertaken to determine the cost-effectiveness of rifaximin versus lactulose. Base case results are presented for rifaximin plus concomitant lactulose versus placebo plus concomitant lactulose (as per the ITT population of the pivotal study, RFHE3001 [rifaximin n=140, placebo n=159]). These are termed as 'rifaximin' and 'placebo' throughout the clinical and economic sections of the submission.

Subgroup analyses were also undertaken on patients in both the rifaximin and placebo arms where all patients received concomitant lactulose (subgroup A, 91.3% of the ITT population [rifaximin n=128, placebo n=145]) and where no patients received concomitant lactulose use (subgroup B, 8.7% of the ITT population [rifaximin n=12, placebo n=14]).

In the base case analysis rifaximin represents a cost-effective treatment option for the reduction in recurrence of episodes of overt HE, at a willingness-to-pay threshold of £30,000 per QALY (ICER £23,186) (Table 1).

Table 1: Base-case cost-effectiveness results

	Rifaximin	**Placebo**
Total costs	£5,168.21	£820.71
Difference in total costs	£4,347.50	
QALYs	1.2179	1.0304
QALY difference	0.1875	
ICER	£23,186	

Abbreviations: LYG, life years gained; QALYs, quality adjusted life year(s); ICER, incremental cost-effectiveness ratio.

Based on the budget impact analysis, it is anticipated that the cost to the NHS in year 1 is approximately £2.5 million, rising to approximately £12.8 million by the end of year 5 (8% uptake rising to 40% uptake). Budget impact calculations are based on drug costs alone, not taking into account any reduction in resource savings and therefore may be overestimated. The pivotal study demonstrated that rifaximin reduces the risk of hospitalisation. It is likely that in clinical practice this will translate into a reduction in emergency admissions and length of hospital stay (24, 25).

In summary, there is currently a considerable unmet need for effective treatments to manage patients with cirrhosis who experience recurrent hepatic encephalopathy. Rifaximin has been shown to significantly reduce breakthrough HE episodes and hospitalisations, compared with placebo, in patients in remission from HE associated with hepatic cirrhosis, therefore offering the potential to improve health related outcomes. Rifaximin appears to offer a potential step change in the management of hepatic encephalopathy, for the NHS, patients and their carers.

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

The technology under assessment is rifaximin-α[4] (550mg BID).

Brand name: TARGAXAN® (also known in other markets as XIFAXAN®, REFERO® and TIXTELLER®)

Approved name: TARGAXAN® 550 mg film-coated tablets

TARGAXAN® contains rifaximin (4-desoxy-4'methyl pyrido (1',2'-1,2) imidazo (5,4-c) rifamycin SV), in the polymorphic form α.

Generic name: Rifaximin

Therapeutic class: intestinal anti-infective agents, antibiotics – ATC code A07AA11

1.2 What is the principal mechanism of action of the technology?

Rifaximin is an antibacterial drug of the rifamycin class that irreversibly binds the beta sub-unit of the bacterial enzyme DNA-dependent RNA polymerase, and consequently inhibits bacterial RNA synthesis. It has a broad antimicrobial spectrum against most of the Gram-positive and Gram-negative, aerobic and anaerobic bacteria, including ammonia producing species. Rifaximin may inhibit the division of urea-deaminating bacteria, thereby reducing the production of ammonia and other compounds that are believed to be important to the pathogenesis of hepatic encephalopathy (HE).

Rifaximin is a non-absorbed antibacterial agent. Pharmacokinetic studies in rats, dogs and humans demonstrated that after oral administration rifaximin in the polymorph α form is poorly absorbed (less than 1%). After repeated administration of therapeutic doses of rifaximin in healthy volunteers and patients with damaged intestinal mucosa (Inflammatory Bowel Disease), plasma levels are negligible (less than 10 ng/mL) (26).

[4] From this point onwards in the submission rifaximin-α is referred to as rifaximin

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

TARGAXAN® is indicated for the reduction in recurrence of episodes of overt hepatic encephalopathy (HE) in patients ≥ 18 years of age.

UK authorisation was received on 10th January 2013.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to marketing authorisation).

Rifaximin is indicated for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age. Section 4.1 of the SPC also states that "In the pivotal study, 91% of the patients were using concomitant lactulose."

Rifaximin has completed the decentralised assessment procedure, with the UK as Reference Member State, and was granted approvable status on 20/11/12.

The RMS Day 210 Final Assessment report states that there are no outstanding clinical, non-clinical or quality issues with the product.

Efficacy

The RMS Day 210 Final Assessment report states that: "The use of rifaximin for the reduction of recurrence of episodes of overt HE is supported by a well-conducted, placebo-controlled phase 3 study, which demonstrated convincing evidence of reduced episodes in the rifaximin group compared to the placebo group. This primary endpoint was also supported by sensitivity analyses and sub group analyses. A long-term study for 24 months showed the efficacy was maintained over this duration."

Notes on the Phase 3 study

The primary efficacy endpoint used in the Phase 3 study was the time to the first breakthrough of overt HE episode (BOHE) (22). (Note that 91.2% of patients in the placebo group and 91.4% of patients in the rifaximin group were receiving lactulose at baseline, and the mean daily doses of lactulose during the study period were stable)

- The proportion of patients remaining in remission at the end of the 6 month study in the rifaximin 550 mg BID group vs. placebo group was 77.9% (109/140) vs. 54.1% (86/159) respectively (22). Conversely, the proportion of patients experiencing a breakthrough episode of HE in the rifaximin 550 mg BID group vs. placebo group was 31/140 (22.1%) vs. 73/159 (45.9%) (22).

- The hazard ratio for the risk of a breakthrough episode in the rifaximin 550mg BID group, as compared with the placebo group, was 0.42 showing a highly significant

protective effect of rifaximin 550mg BID + lactulose (95% confidence interval [CI], 0.28 to 0.64) P<0.001 (22).

- The degree to which rifaximin 550mg BID + lactulose reduced the risk of a breakthrough episode was consistent across subgroups (22).

The key secondary efficacy endpoint was defined as: “Hospitalisation because of the disorder or hospitalisation during which an episode of HE occurred." (22).

- The proportion of patients with no hospitalisation related to HE at the end of the 6 month study in the rifaximin 550 mg BID group vs. placebo group was 86.4% (121/140) vs. 77.4% (123/159) respectively. Conversely, the proportion of patients requiring hospitalisation related to HE in the rifaximin 550 mg BID group vs. placebo group was 19/140 (13.6%) vs. 36/159 (22.6%) (22).

- The hazard ratio for the risk of a HE-related hospitalisation in the rifaximin group, as compared with the placebo group, was 0.50 showing a highly significant protective effect of rifaximin (95% CI, 0.29 to 0.87) P = 0.0129) (22).

Notes on the long-term study

Patients from the Phase 3 study were permitted to enter a 24 month open label extension (OLE) study upon completion or withdrawal from the initial 6 month study, provided they had a Conn (West Haven) score of ≤2. Subjects who experienced HE or associated symptoms during or after the RFHE3001 study were considered eligible for entry into this open-label study if the subject and investigator did not perceive study medication as a possible cause of the HE episode or associated symptoms. New subjects who met the eligibility criteria (≥1 previous HE episode with a Conn score of ≥2 within the past 21 months) were also enrolled (23). Overall, 322 patients entered the study. All received rifaximin 550 mg twice daily; concomitant lactulose use was also permitted and follow-up clinic visits were scheduled every 3 months.

Similar HE breakthrough event rates to the Phase 3 study were observed, with long term rifaximin 550mg BID treatment similar to the RCT rifaximin 550mg BID group (0.6/ person exposure years), and significantly lower than RCT placebo group (1.59/ person exposure years, p <0.0001).

Safety

The RMS Day 210 Final Assessment report states that: “Post-marketing pharmacovigilance surveillance has not raised any demonstrable safety concerns” for rifaximin in relation to its approval for the treatment of HE in 10 countries, and as adjunctive therapy for the treatment of hyperammonemia in 12 countries worldwide.

Adverse events in the Phase 3 study

The incidence of adverse events reported during the Phase 3 study was similar in the rifaximin 550mg BID group (80.0%) and the placebo group (79.9%), as was the incidence of the more common serious adverse events (22).

The report notes that “There is a high incidence of side effects seen in the clinical trials. These have been mentioned under appropriate sections of the SPC as well as covered in the risk management plan.” It should be noted that 91.2% of patients in the placebo group and 91.4% in the rifaximin 550mg BID group were receiving lactulose at baseline (22). The frequency of Treatment-Emergent Adverse Events (TEAEs) was similar between the rifaximin 550mg BID group and the placebo treatment group. Also AEs and laboratory findings were as expected based on the population of subjects with chronic liver disease who were receiving lactulose therapy, in that common AEs included diarrhoea, nausea, peripheral oedema and anaemia.

Norgine have a very minimal risk management plan, alongside standard pharmacovigilance.

Risk-benefit assessment

The Risk-Benefit Assessment in the RMS Day 210 Final Assessment report is as follows:

“The use of rifaximin for the reduction of recurrence of episodes of overt HE is supported by a well-conducted, placebo-controlled phase 3 study, which demonstrated convincing evidence of reduced episodes in the rifaximin group compared to the placebo group. This primary endpoint was also supported by sensitivity analyses and sub group analyses. A long-term study for 24 months showed the efficacy was maintained over this duration. There is a high incidence of side effects seen in the clinical trials.* These have been mentioned under appropriate sections of the SPC as well as covered in the risk management plan.

There are limited effective options available for the treatment of HE. Rifaximin has been approved and used in a number of European countries and US. Published literature also supports the use of rifaximin in HE.

Therefore based on the submitted data the benefit-risk ratio is considered favourable.”

* Note: The frequency of Treatment-Emergent Adverse Events (TEAEs) was similar between the rifaximin 550mg BID group and the placebo treatment group. Also AEs and laboratory findings were as expected based on the population of subjects with chronic liver disease who were receiving lactulose therapy, in that common AEs included diarrhoea, nausea, peripheral oedema and anaemia (27).

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

In the UK, TARGAXAN® is indicated for the reduction in recurrence of episodes of overt hepatic encephalopathy (HE) in patients ≥ 18 years of age. Section 4.1 of the SPC also features the wording: “In the pivotal study, 91% of the patients were using concomitant lactulose.”

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

No Norgine-sponsored studies are expected to provide additional evidence during the next 12 months.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Rifaximin was launched on the 28th January 2013.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Rifaximin has completed the decentralised assessment procedure, with the UK as Reference Member State, and was granted approvable status on 20/11/12.

Rifaximin was registered in Australia by the TGA on 17 May 2012 and received marketing approval in the U.S. in March 2010.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Rifaximin is not subject to any form of HTA in the UK at the time of writing. Submission to the SMC is anticipated on March 28th 2013. Submission to the AWMSG is not required as rifaximin meets with one of their exclusion criteria.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 2: Unit costs of technology being appraised

Pharmaceutical formulation	550 mg film-coated tablets
Acquisition cost (excluding VAT)	NHS Price £259.23 for a 56 tablet pack.
Method of administration	Oral
Doses	Recommended dose: 550 mg twice a day
Dosing frequency	Twice daily
Average length of a course of treatment	6 months. Treatment beyond 6 months should take into consideration the individual balance between benefits and risks, including those associated with the progression of hepatic dysfunction
Average cost of a course of treatment	Based on 6 months treatment the anticipated cost will be £1689.65. Based on clinical need an annual cost will be £3379.29 for 365 days.
Anticipated average interval between courses of treatments	Not anticipated
Anticipated number of repeat courses of treatments	None
Dose adjustments	No dosage adjustment needed in: • Elderly patients and patients with renal insufficiency • Patients with hepatic insufficiency Use with caution in patients with severe hepatic impairment and in patients with MELD (Model for End-Stage Liver Disease) score > 25 (TARGAXAN® SPC)

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

No.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

In the pivotal 6-month, double-blind, multi-centre, randomised, placebo controlled trial to evaluate the efficacy and safety of rifaximin 550mg BID, for the maintenance of remission from episodes of HE in outpatients with a recent history of recurrent, overt HE, 91% of the patients were using concomitant lactulose (22).

2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Summary

- The term HE encompasses a spectrum of neuropsychiatric abnormalities seen in patients with established liver disease, and is most commonly associated with liver cirrhosis (1, 2).
- Symptoms range from subtle neurological abnormalities (e.g. mood alterations, changes in reaction times in daily activities such as driving), to severe neurological impairment (e.g. difficulty in moving and communicating) and in extreme cases, coma (2-4).
- Approximately 70% of patients with cirrhosis present with subclinical or mild HE, and 23-40% may progress to a more severe form of the disease (15-17). Development of HE is predictive of poor survival in cirrhosis (28, 29).
- HE is associated with diminished health related quality of life across both physical and mental domains (5-10), and with a substantial burden on carers (11).
- Acute episodes usually involve hospitalisation. Once in remission, patients typically receive long-term treatment with lactulose in an effort to prevent recurrence of episodes.

The term HE encompasses a spectrum of neuropsychiatric abnormalities seen in patients with established liver disease, and is most commonly associated with liver cirrhosis (1, 2). Patients with HE may experience symptoms ranging from subtle neurological abnormalities (e.g. mood alterations, changes in reaction times in daily activities such as driving), to severe neurological impairment (e.g. difficulty in moving and communicating) and in extreme cases, coma (2-4).

Liver cirrhosis

Cirrhosis is the end result of liver damage caused by chronic liver disease, and consists of the thickening and scarring of connective tissue (fibrosis) throughout the liver (30). In developed countries, the most common causes of cirrhosis are excessive alcohol intake, hepatitis C, and non-alcoholic steatohepatitis (the most extreme form of non-alcoholic fatty liver disease NAFLD) (30, 31). The progression and outcome of cirrhosis is essentially the same whatever the cause.

There are two main, sequential stages of cirrhosis: compensated and decompensated cirrhosis (31, 32). In compensated cirrhosis hepatic function is stable and no complicating factors of cirrhosis are present. Patients may not display any obvious symptoms of liver disease. The persistent activation of the fibrogenesis pathway, and the

continued loss of liver function, eventually lead to decompensated cirrhosis, in which the liver can no longer maintain its essential functions (32). Decompensated cirrhosis is characterised by the development of life-threatening complications such as variceal haemorrhage, HE and ascites (32).These complications are all associated with a poor prognosis, reflecting a steady decline in hepatic function (31).

Hepatic encephalopathy

Approximately 70% of patients with cirrhosis present with subclinical or mild HE, and 23-40% may progress to a more severe form of the disease (15-17).

Classification

A 1998 classification of HE by the Organisation Mondiale de Gastroentérologie Working Party (33) has been widely used in the literature. The working party agreed that the term HE reflects a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction, “after the exclusion of other known brain disease”. It established a classification system that proposes three main HE “types” (33):

- **Episodic HE** describes the most common form of HE, where a disturbance of consciousness develops in previously stable patients over hours to days, but does not persist. Patients with episodic HE may return to normal following an acute episode. However, some will retain a degree of impairment in the longer term (or between episodes). Patients may go on to develop further episodes of HE (33, 34).

- **Persistent HE** describes patients whose HE symptoms remain stable over a long period and who typically do not revert to a normal mental status.

- **Minimal HE** is the term used to describe patients with cirrhosis who appear to be clinically normal but show slight abnormalities of cognition and/or neurophysiological variables. These abnormalities may manifest only as subtle changes in reaction times in complex daily activities such as driving, but can have a detrimental impact on HRQoL and may predispose to the development of overt HE (33, 34).

Rifaximin is to be used in the management of patients, ≥ 18 years of age, for the reduction in recurrence of episodes of overt HE. Section 4.1 of the SPC also features the wording: “In the pivotal study, 91% of the patients were using concomitant lactulose.”

Symptoms

Signs and symptoms of HE include personality changes, intellectual impairment, reduced level of consciousness and altered neuromuscular activity (4).

Hepatic encephalopathy can be graded using the Conn score (also called the West Haven classification) (35) in which higher scores indicate a higher severity, as follows:

- Grade 0: no personality or behavioural abnormality detected.

- Grade 1: lack of awareness, euphoria or anxiety, shortened attention span, impaired performance of addition.

- Grade 2: lethargy or apathy, minimal disorientation for time or place, subtle personality change, inappropriate behaviour, impaired performance of subtraction.

- Grade 3: somnolence to semi stupor but responsive to verbal stimuli, confusion, gross disorientation.

- Grade 4: coma (unresponsive to verbal or noxious stimuli).

In 2011, the ISHEN classification system (34) was proposed, but is yet to be fully adopted by the scientific community. It classifies patients as being “unimpaired” (no clinical neurophysiological/neuropsychometric changes), having “covert” HE (patients with minimal HE or HE with a Conn score of 1) or having “overt” HE (patients with HE with a Conn score of 2, 3 or 4 as graded by the West Haven Criteria).

Burden of hepatic encephalopathy on patients and carers

Hepatic encephalopathy is associated with diminished health related quality of life (HRQoL) across both physical and mental domains (5-10).

- Impairment of HRQoL is correlated with repeat hospitalisations and liver disease severity, as well as episodes of HE (10).

- HRQoL in patients with chronic liver disease is considerably lower than that of the general population, and is similar to that observed in patients with other chronic diseases, such as congestive heart failure (5). The more severe the disease, the poorer the HRQoL (5).

- Impaired HRQoL as measured by the Chronic Liver Disease Questionnaires (CLDQ) has been found to be correlated with the occurrence of breakthrough overt HE episodes. Patients who experienced overt breakthrough HE had a significantly lower overall HRQoL score than patients who maintained remission from overt HE (10).

Hepatic encephalopathy may also affect quality of life in caregivers. As HE can cause patients to become confused, unable to complete simple tasks and even unable to communicate, such patients will often require substantial help from a caregiver to ensure that they can manage to complete their daily activities (4, 11). Bajaj et al. 2011 (11) interviewed caregivers of two sets of patients with cirrhotic liver disease – those who had experienced previous HE and those who had not. Patients with previous HE were a significantly higher burden on their caregivers, with specific effects on schedule, sense of entrapment, and personal health. Previous HE also negatively affected the employment capability and financial status of patients. Of interest, there was a direct correlation between key cognitive tests and burden on caregivers (11).

Pathogenesis

Although the precise mechanisms that lead to the development of HE are yet to be fully characterised, the neuropsychiatric symptoms are thought to result from elevated blood levels of a number of gut-derived neurotoxins, in particular ammonia (36).

The normal bacteria of the gut convert ingested protein into ammonia and other toxins, which enter the blood (36). In individuals with normal hepatic function, ammonia in the blood is converted to urea by the liver and is subsequently excreted in the urine. In patients with severely impaired liver function, or in whom blood does not circulate through the liver in the normal way (e.g. with a portosystemic shunt), ammonia is not degraded by the liver and instead enters the systemic circulation, leading to high blood ammonia levels (36). The ammonia and other toxins cross the blood-brain barrier. This leads to a general disruption of communication in the brain, which is thought to lead to the symptoms observed in patients with HE (1, 4, 36).

Disease course

Hepatic encephalopathy is a progressive condition, with up to 50% of patients with minimal HE developing overt HE (i.e. a symptomatic episode of HE) within 3 years (1-3).

Hepatic encephalopathy has been observed to have a negative effect on survival. In a systematic review, d'Amico et al. found that "By far, the most consistent and 'robust' predictor of death in cirrhosis is the Child–Pugh score and/or its components (albumin, bilirubin, ascites, encephalopathy and prothrombin time)" (28).

Alvarez et al. found that development of HE at any time during follow-up independently correlated with survival in a cohort of 165 patients with decompensated alcoholic cirrhosis. Alvares reported a median survival after onset of HE of only 14 months (95% CI: 5-23) (29).

Jepsen et al. 2010 (19) investigated the clinical course of alcohol-related cirrhosis in a cohort of 466 Danish patients by conducting a retrospective medical chart review. One-year mortality was 17% among patients with no initial complications and 64% following HE, showing clearly the high mortality associated with HE, compared with cirrhosis that is not accompanied by complications (19). A retrospective review by Bustamante et al. examined the survival rates of 111 cirrhotic patients who developed a first episode of acute HE. During the follow-up period (12-17 months), 82 patients (74%) died. In this study the survival of patients who experienced a first episode of HE was 42% at 1 year of follow-up and 23% at 3 years (12, 37).

The symptoms of HE can usually be reversed, either fully or partially, by appropriate treatment. However, patients who have had one episode are at risk of developing episodic recurrences, even in the absence of known precipitating factors (18).

Most patients with symptomatic chronic liver disease will experience progressive deterioration of liver function, further reducing the liver's ability to deal with toxins and increasing the likelihood of further episodes of HE.

Epidemiology

No specific information on the incidence or prevalence of HE in the UK could be found.

Approximately 70% of patients with cirrhosis present with subclinical or mild HE, and 23-40% may progress to a more severe form of the disease (15-17).

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

The number of patients with recurrent episodes of HE in England and Wales is uncertain. Chronic liver cirrhosis is caused by several different conditions. Statistics are collected separately for each, and the occurrence of episodes of HE does not appear to be recorded systematically. No specific information on the incidence or prevalence of HE in the UK could be found.

A study published in 2008 using information from the General Practice Research Database reported that the crude incidence of liver cirrhosis in the UK was 16.99 per 100,000 person years in 2001 (38). The prevalence of cirrhosis was an estimated 76.3 per 100,000 population aged over 25 in mid-2001 (38).

Approximately 70% of patients with cirrhosis present with subclinical or mild HE, and 23-40% may progress to a more severe form of the disease (15-17). Based on the incidence and prevalence of cirrhosis referred to above, a crude calculation based on the prevalence above suggests that there are approximately 33,723 patients with cirrhosis in England and Wales. Of these, 23,606 may have subclinical or mild HE, and 5,429-9442 may progress to a more severe form of the disease (based on a total population of 44,197,700 above the age of 18 in England and Wales) and therefore eligible for treatment (39).

Fleming et al. 2008 (38) reported a statistically significant increase in incidence of both alcoholic cirrhosis and non-alcohol-related cirrhosis during the period 1992 to 2001, with an overall increase of 45% (38). The incidence of HE is expected to rise in line with the rising prevalence of cirrhosis, so the number of patients estimated above is likely to be an underestimate. In the U.S. in 2004 over 50,000 patients were hospitalised with HE (40).

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

No specific information on life expectancy of patients with recurrent episodes of HE in England and Wales could be found.

A retrospective review by Bustamante et al. 1999 (12) examined the survival rates of 111 cirrhotic patients who developed a first episode of acute HE. During the follow-up period (12-17 months), 82 patients (74%) died. In this study the survival of patients who

experienced an episode of HE was 42% at 1 year of follow-up and 23% at 3 years (12, 37).

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

No NICE guidance or protocols were found.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

At the time of writing there are no recognised diagnostic pathways or treatment guidelines for HE. The typical care pathway in England and Wales was discussed with a number of UK liver specialists and the discussions were used to inform this section.

Management of hepatic encephalopathy

The key management goals for HE are (18):

- Provision of supportive care.
- Identification and removal of precipitating factors.
- Reduction of nitrogenous load (e.g. ammonia) in the gut.

Patients with HE due to chronic liver cirrhosis are generally managed in secondary care, as there is a lack of awareness and knowledge of HE in primary care and in the community.

Most patients are generally seen in hepatology or gastroenterology outpatient clinics every 3-6 months for review of their HE and/or underlying liver disease severity. If a patient has recently been discharged from hospitalisation for an acute episode of HE they will also have an additional follow-up visit 4 weeks after discharge.

Patients are in either of two states of HE: the ISHEN classification groups together patients with minimal HE and grade 1 HE under the label “covert HE”, and patients with grade 2,3 or 4 HE as “overt HE” (34). However, expert advisors noted that in UK clinical practice the terms covert and overt are not commonly used. Patients are often referred to as having minimal HE or clinically relevant HE.

Whilst a patient is in remission or experiencing minimal HE symptoms they may be managed effectively at home independently or by their family or carer.

However, if a patient experiences an acute “overt” episode they may be admitted to hospital for active management and treatment.

Acute episode of hepatic encephalopathy

Most patients will be admitted to hospital via Accident and Emergency (particularly if they are newly diagnosed) or through a Medical Admissions Unit (if they are known as patients with cirrhosis or HE as they will be referred in by a GP or another health care professional).

Approximately 80% of patients admitted to hospital have grade 2 or grade 3 HE, with grade 2 representing the most common presentation.

Management of HE primarily begins with a thorough examination for the presence of precipitating factors that may be triggering or exacerbating the condition. Common precipitating factors include gastrointestinal bleeding, infection, constipation, electrolyte imbalance and excess dietary (especially animal) protein intake. If identified, precipitating factors should be avoided, corrected or appropriately managed in order to limit their effect on the development of HE (41, 42).

Pharmacological management

The major pharmacological treatments for HE target the production and absorption of bacterially-derived neurotoxins, particularly ammonia (4). Treatments consist of non-absorbable disaccharides, such as lactulose and lactitol, and antibiotics (used outside of their licensed indications).

Non-absorbable sugars or disaccharides (lactulose and lactitol) are considered the first-line therapy for HE and are believed to act by reducing ammonia production by gut bacteria and by reducing the absorption of ammonia through the intestinal wall into the blood, which reduces the ammonia eventually reaching the brain in patients with compromised liver function (4, 43).

Clinical advice indicates that enemas and lactulose are given to almost all patients hospitalised with an episode of HE. Macrogol is sometimes used instead of lactulose.

Antimicrobials have a long history of use in the management of HE, particularly when patients have failed to respond, or are intolerant, to non-absorbable disaccharides (43). Antimicrobials act by selectively eliminating urease-producing organisms from the intestinal tract, which reduces the production of ammonia and therefore reduces the ammonia entering the blood (4).

Theoretically, antimicrobials that are poorly absorbed across the intestines are most suited to the treatment of HE, as the aim is to selectively inhibit or eliminate gut bacteria without the risk of inducing significant systemic side effects or promoting antibiotic resistance in populations of bacteria located in body systems outside of the gut (4).

A short trial of neomycin is sometimes used to manage acute episodes of HE. It is noted that neomycin is associated with the risk of ototoxicity and nephrotoxicity when used for prolonged periods, and there are a number of warnings specified in the SPC for neomycin relating to hepatic impairment and to long-term use (21).

A number of patients will also be assessed for their eligibility for liver transplant. There are eligibility criteria that relate to HE but the majority of patients become eligible due to the severity of their underling liver disease. The clinical advisors indicate only 10% of HE patients fulfill the eligibility criteria to gain a place on the transplant waiting list.

Length of hospital stay

The average length of stay varies depending on the precipitating cause of the HE episode. This was estimated at 3–5 days (in simple cases) and >10 days to 1 month for more complicated cases such as patients with sepsis.

Some patients suffering from a severe HE episode will require an Intensive Care admission.

The average length of the whole HE episode for a simple case was estimated at approximately 10–12 days (UK liver specialists opinion), but this is highly variable and a patient may take up to 6 weeks to recover.

Long term management of patients who have had prior episodes of hepatic encephalopathy and are currently in remission

Once patients are discharged from hospital, the current long term management generally includes the use of daily lactulose and enemas.

There are currently no UK or European licensed treatments for the reduction in recurrence of episodes of overt HE. However, lactulose is the current standard of care and is the most routinely used long term therapeutic option for patients with HE at this time.

Rifaximin is the first and only treatment in the UK licensed for the reduction in recurrence of episodes of overt HE in patients ≥ 18 years of age (26).

As section 4.1 of the SPC states, in the pivotal study, 91% of the patients were using concomitant lactulose (26).

Expected changes with the use of rifaximin

Rifaximin is the only treatment that has been shown to reduce the recurrence of episodes of overt HE, and hospitalisation due to HE, compared to placebo (91% patients were taking concomitant lactulose). The 6 month randomised, double blind, placebo-controlled phase 3 pivotal study conducted in patients in remission from chronic liver disease showed that:

- Rifaximin 550 mg BID plus lactulose significantly reduced ($p<0.001$) the relative risk of recurrence of overt HE episodes by 58% (absolute risk reduction 23.8%) vs. placebo plus lactulose over 6 months (22).

- Rifaximin 550 mg BID plus lactulose significantly reduced (p=0.01) the relative risk of hospitalisation involving HE by 50% (absolute risk reduction 9%) vs. placebo plus lactulose over 6 months (22).

- Additionally, it has been shown that long term treatment over 24 months with rifaximin 550 mg BID plus lactulose afforded continued protection from HE, reduced the hospitalisation rate, and did not adversely affect safety or mortality in patients with cirrhosis (23).

Rifaximin is indicated for the reduction in recurrence of episodes of overt HE in patients ≥ 18 years of age. In the pivotal study, 91% of the patients used concomitant lactulose (26).

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Evidence-based guidelines on the treatment of HE are lacking, due to the poor quality of the evidence base (18).

UK liver specialists highlighted that there was variability in the provision of care for patients with HE and there was inequity in the provision of or access to rifaximin in the management of the condition.

2.7 Please identify the main comparator(s) and justify their selection.

The main comparators in the final scope are: lactulose; neomycin; and neomycin with lactulose.

- Lactulose is considered by Norgine to be an appropriate comparator, and lactulose has been used as the comparator in the economic model. Ninety one percent of patients in the pivotal study used concomitant lactulose and patients in clinical practice receive lactulose maintenance therapy routinely.

- In the UK neomycin is licenced for hepatic coma but it is not licenced for the reduction in recurrence of episodes of overt HE.

- The SPC for neomycin carries the following warnings relating to hepatic impairment and to long-term use (21), which Norgine considers make it inappropriate as a comparator in long-term treatment for the prevention of HE recurrences:

    - Impaired hepatic function or auditory function, bacteraemia, fever, and possibly exposure to loud noises have been reported to increase the risk of ototoxicity, while volume depletion or hypotension, liver disease, or female sex have been reported as additional risk factors for nephrotoxicity.

    - When used as an adjunct in the management of hepatic coma, care should be taken that administration is of the minimal period necessary, since prolonged exposure to the drug may result in malabsorption.

- Since prolonged therapy may result in the overgrowth of non-sensitive organisms, treatment should not be continued longer than necessary to prevent superinfection due to the overgrowth of non-sensitive organisms.

- There are currently no clinical data to support the use of neomycin in the reduction of recurrence of HE in patients ≥ 18 years of age (see section 6.2). No controlled trials with neomycin have demonstrated equal or superior efficacy to lactulose in the patient population of interest in this submission.

- There is no clinical data in the literature to support the use of neomycin in combination with lactulose and this is a new addition to the comparator section of the final scope.

- Neomycin would appear not to be routinely used in clinical practice in the prevention of recurrence of in patients in remission. Based on neomycin usage in Primary Care in England in 2011 (as sourced from Prescription Cost Analysis via the NHS Information Centre) there were only 29 prescriptions of Neomycin Tablets 500mg issued in the year 2011, and 2,320 tablets used. Furthermore, as the data source does not specify an indication we believe that this usage is likely to be across a number of different indications. Norgine considers that overall neomycin usage is minimal and it should therefore not be included as a comparator. This was confirmed by UK liver specialists.

Neomycin and neomycin with lactulose is therefore not considered by Norgine to be a comparator and during consultation had requested neomycin to be removed from the final scope.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

It is not normally necessary to prescribe any therapies to manage adverse reactions associated with rifaximin.

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Rifaximin is an orally administered tablet and can be taken by patients at home. No special tests or monitoring are required, beyond the routine follow-up care expected for patients with HE.

2.10 Does the technology require additional infrastructure to be put in place?

No.

3 Equality

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology
could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

3.1.2 Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

No such issues have been identified.

3.1.3 How has the analysis addressed these issues?

Not applicable.

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Rifaximin is an established technology that brings innovation to the treatment pathway for HE. Recurrent HE episodes are a distressing aspect of chronic liver disease for both patients and carers, entail considerable use of NHS resources in the form of hospitalisations, and may be associated with a poorer prognosis for the patient in terms of increased mortality (12, 14, 18-20). Reduction in recurrence of episodes of overt HE is therefore an important goal in the treatment for patients with liver disease.

Lactulose is the current standard of care and is routinely used in clinical practice for management of HE. A Phase 3 study (22) demonstrated that rifaximin 550 mg twice daily plus lactulose (over a 6-month period as compared with placebo plus lactulose) had the following benefits:

- Significantly reduced the risk of an episode of HE: hazard ratio for a breakthrough episode in the rifaximin group vs placebo group was 0.42 (95% CI, 0.28 to 0.64; P<0.001) (22).

- Significantly reduced the risk of hospitalisation due to HE: the hazard ratio for HE-related hospitalisation in the rifaximin group vs placebo group was 0.50 (95% CI, 0.29 to 0.87; P = 0.0129) (22).

- Significantly improved the health related quality of life, (HRQoL) as measured by the Chronic Liver Disease Questionnaire (CLDQ): during remission the rifaximin 550mg BID group had consistent improvements in HRQoL measures, of both clinical importance and statistical significance, across each of the six domains and overall when compared with the placebo group (due to altered mental and neuromotor status subjects experiencing an episode of HE were unable to complete the CLDQ assessment) (10).

The study shows the superiority of rifaximin therapy plus lactulose over treatment with placebo plus lactulose, and a significant treatment effect was noted within 28 days after randomisation.

In summary, there is currently a large unmet need for effective treatments to manage patients with cirrhosis who experience HE. Rifaximin has been shown to significantly reduce breakthrough HE episodes and hospitalisations, compared with placebo (approximately 90% were also taking lactulose) in patients in remission from HE associated with hepatic cirrhosis, therefore offering the potential to improve health related outcomes.

Rifaximin appears to offer a potential step change in the management of the condition, both for the NHS and for patients.

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

We believe that there are potentially substantial health related benefits that are unlikely to be included in the QALY calculation. These include the impact on the following HRQoL domains as demonstrated by the CLDQ; abdominal symptoms, fatigue, systemic symptoms, activity, emotional function and worry (10, 22). These also include the impact on the health and quality of life of carers.

In a randomised controlled study of patients in remission from recurrent HE, resulting from chronic liver disease, the Chronic Liver Disease Questionnaire (CLDQ) was administered to a sub-population of 219 patients from the USA and Canada:

- Significant differences in health-related QoL (HRQoL) were seen in patients experiencing breakthrough HE episodes, compared with those who remained in remission, as determined by time-weighted average Chronic Liver Disease Questionnaire (CLDQ) scores (10).

- Higher HRQoL scores were noted across all domains in the group of patients in remission from HE episodes (10).

- Across all domains there were significant improvements in the HRQOL* of patients who were in remission in the rifaximin 550 mg BID group (n=75) compared with those in the placebo group (n=59) (10).

*As determined by differences in least square means of time-weighted average CLDQ scores.

The variable length and nature of episodes of HE make capturing quality of life difficult in this patient population. For example, a patient whose episode is measured as a West Haven score of grade 3, may no longer be able to accurately describe their own quality of life at that specific time point. In addition, clinical opinion suggests that a patient's quality of life diminishes over time as a result of recurring episodes and as their liver function declines.

Reducing the recurrence of HE symptoms is likely to have a significant benefit for the carers of patients with advanced liver disease, given the anxiety and difficulty caused to carers by having to deal with neuropsychiatric symptoms in the patient suffering from a HE episode.

Bajaj et al. 2011 (11) interviewed caregivers of two sets of patients with cirrhotic liver disease – those who had experienced previous HE and those who had not. Patients with previous HE were a significantly higher burden on their caregivers, with specific effects on schedule, sense of entrapment, and personal health. Previous HE also negatively affected the employment capability and financial status of patients. Of interest, there was a direct correlation between key cognitive tests and burden on caregivers (11) .

It is likely that a reduction in HE episodes and hospitalisations will have a beneficial effect on carer burden and consequently on their health related quality of life, although this has not yet been assessed as part of a formal study.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

These judgements are based on data from the pivotal Phase 3 study (22, 44) and a patient and carer burden study in cirrhosis and HE (11).

5 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults who have had prior episodes of HE and are currently in remission	Adults with chronic liver disease who have had prior episodes of overt HE and are currently in remission	The indication and submission do not cover patients with HE which is caused by an acute liver insult.
Intervention	Rifaximin	Rifaximin, plus concomitant lactulose (as per ITT population in RFHE3001)	
Comparator(s)	Lactulose Neomycin Neomycin with lactulose	Placebo plus concomitant lactulose (as per ITT population in RFHE3001)	(See Section 2.7 for details) Neomycin is not licensed for the indication. Neomycin is not commonly used in clinical practice for long-term prevention of HE recurrence. The neomycin SPC contains warnings against long-term use. There is no evidence for the efficacy of neomycin or neomycin and lactulose in combination in this indication.
Outcomes	Disease progression to more severe grade of HE Frequency of hospitalisation, and time until next hospitalisation Frequency of recurrent acute episodes of HE and time to next episode	Disease progression to more severe grade of HE Frequency of hospitalisation, and time until next hospitalisation Frequency of recurrent acute episodes of HE and time to next episode Mortality	

	Mortality Adverse effects of treatment Health-related quality of life	Adverse effects of treatment Health-related quality of life	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As stipulated in the NICE scope	
Subgroups to be considered	None specified	None specified	
Special considerations, including issues related to equity or equality	If evidence allows, consideration will be given to rifaximin given with or without concomitant medications, such as lactulose. If evidence allows, the effectiveness will be assessed by severity of liver failure. Guidance will only be issued in accordance with the marketing authorisation.	If evidence allows, consideration will be given to rifaximin given with or without concomitant medications, such as lactulose. Guidance will only be issued in accordance with the marketing authorisation.	There is no evidence that the effect of rifaximin is variable in subgroups assessed by severity of liver failure

Section B – Clinical and cost effectiveness

6 Clinical evidence

Evidence for the efficacy and safety of rifaximin is taken from the pivotal RCT (RFHE3001) and from a long-term open-label single extension arm study (RFHE3002). A summary of efficacy from these studies is presented below. A summary of safety is provided in section 6.9

Efficacy - Pivotal, double-blind, randomised study RFHE3001 (22, 27)

- In RFHE3001, rifaximin treatment resulted in a 58% reduction in the risk of experiencing a breakthrough overt HE episode during the course of the study, compared with placebo (HR 0.42: 95% CI 0.28 to 0.64) (p<0.001).
  - Several strong independent predictors of experiencing a breakthrough overt HE episode (baseline age, MELD score, duration of current verified remission, and number of prior HE episodes) were considered in covariate analyses. The treatment effect of rifaximin was maintained in the presence of these statistically significant competing factors.
  - Sensitivity analyses, considering patients with comorbid conditions and those using concomitant medications separately, also showed significant hazard ratio reductions with rifaximin versus placebo.
  - The effect of rifaximin treatment in reducing the risk of experiencing breakthrough overt HE episodes during the 6-month treatment period was consistent across all subgroups analysed (geographical, sex, age, race, baseline MELD score, baseline Conn score, prior lactulose use, diabetes).
- Subjects in the rifaximin group had a 50% reduction in the risk of hospitalisation due to HE during the 6-month treatment period when compared with placebo (HR 0.500 (95% CI: 0.29 to 0.873) (p=0.01).
- Rifaximin treatment resulted in highly significant reductions in the risk of experiencing an increase in Conn score (53.7%, p<0.0001).
- Where episodes of overt HE did occur, they were more severe (as indicated by a greater change in Conn score compared with baseline) among placebo patients compared with rifaximin.

Efficacy - Open-label, single-arm extension study RFHE3002 (45)

- Long-term (24 months) treatment with rifaximin did not result in loss of effect regarding reduction in the risk of experiencing breakthrough overt HE episodes (23).
- All HE breakthrough rates with long term rifaximin treatment were similar to the RCT rifaximin group (0.6), and significantly lower than RCT placebo group (1.59, p <0.0001) demonstrating the long term durability and repeatability of the protective effect of rifaximin from HE breakthrough (23).
- Conn scores and asterixis grades were generally maintained or improved with

rifaximin use up to 36 months (45).

- Long term treatment with rifaximin 550 mg BID afforded continued protection from HE, reduced the hospitalization rate, and did not adversely affect safety or mortality in patients with cirrhosis (23).

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in Section 10.2, appendix 2.

A systematic review was conducted to identify relevant randomised controlled trials from the published literature regarding the efficacy and safety of rifaximin, lactulose and neomycin. The population of interest in the systematic review was relevant to the decision problem (i.e. adults who have had prior acute episodes of HE and were receiving treatment in order to reduce recurrent episodes of HE). Searches of the main databases were supplemented by hand searching.

The search strategy is provided in Section 10.2.

Lactulose is considered to be the only comparator of relevance to this submission. The rifaximin pivotal trial (RFHE3001) provides direct evidence for this comparison (as 91% of patients in the pivotal trial received concomitant lactulose).

Therefore, the systematic review only included lactulose to identify lactulose studies that may form part of a network to facilitate an indirect comparison /network meta-analysis (NMA) of rifaximin versus neomycin and/or rifaximin versus lactulose and neomycin.

A separate review of the unpublished data from the manufacturer database was also undertaken to identify any relevant unpublished data in the population of interest (i.e. adults who have had prior acute episodes of HE).

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Studies identified were initially assessed based on title and abstract. Papers not meeting the inclusion criteria were excluded, and allocated a “reason code” to document the rationale for exclusion. Papers included after this stage were then assessed based on the full text; further papers were excluded, yielding the final data set for inclusion. The final included data set consisted of clinical studies for rifaximin and those for comparator treatments. The full text of these comparator studies was screened and those suitable for indirect comparison were selected.

Inclusion and exclusion selection criteria are shown in Table 3.

Table 3: Eligibility criteria used in search strategy

	Description	Justification
Inclusion criteria		
Population	Adults who have had prior acute episodes of HE (grade II to IV), types A, B and C.	Population of interest in final scope
Interventions	Rifaximin, neomycin and lactulose	Interventions and comparators identified in final scope
Outcomes	• Disease progression to more severe grade of HE • Frequency of hospitalisation • Frequency and severity of recurrent acute episodes of HE • Mortality • Adverse effects of treatment • Health-related quality of life • Rate of liver transplantation	Outcomes outlined in the draft scope and covering all outcomes included in the final scope
Study design	Clinical studies limited to Phase II or III randomised controlled trials. It is proposed that both double-blind and open-label RCTs should be included	To identify RCT data
Language restrictions	English abstracts of non-English publications will be included.	To reduce number of hits and to identify studies in patient populations relevant to the UK setting
Exclusion criteria		
Population	Subjects <18 years of age, who had not had prior acute episodes of HE (grade II to IV), types A, B and C	Not relevant to final scope
Interventions	Non-relevant comparators	Not relevant to final scope
Outcomes	Studies not investigating efficacy, safety or quality of life	Not relevant to final scope
Study design	Any studies that were not randomised controlled studies i.e. cohort, case series, registries	To identify the highest level of evidence
Language restrictions	Abstracts and publications in non-English language	To reduce number of hits and to identify studies in patient populations relevant to the UK setting

Abbreviations: HE, hepatic encephalopathy; RCT, randomised controlled trial.

6.2.2 A flow diagram of included and excluded studies at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses. Such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in Section 6.2.4.

The systematic review identified 322 potentially relevant (non-duplicate) publications. Citations were screened by title and abstract (1st pass), resulting in 252 exclusions. A total of 70 publications were selected for full-text review; of these 53 publications were excluded (see Table 72 in Appendix, Section 10.2, resulting in a total of 18 publications, including one hand-searched publication (12 full papers and 6 abstracts)

- Full papers (n=12)
  - Rifaximin (n=4): Bass et al, 2010 (22), Loguerico et al, 2003 (46), Paik et al, 2005 (47), Sanyal et al, 2011 (10)
  - Lactulose (n=8): Bresci et al, 1993 (48), Elkington et al, 1969 (49), Heredia et al, 1988 (50), Loguerico et al, 1995 (51), Poo et al, 2006 (52) , Raza et al, 2004 (53), Sharma et al, 2009 (54), Takuma et al, 2010 (55)
- Abstracts (n=6)
  - Rifaximin (n=6): Bass et al, 2009 (56), Brown et al, 2009 (57), Mullen et al, 2009 (58), Poordad et al, 2009 (59), Sanyal et al, 2009 (60), Sanyal et al, 2010 (61)

The 18 publications were reported from 11 studies:

- Rifaximin studies (n=3): Bass et al, 2010 (22), Loguerico et al, 2003 (46), Paik et al. 2005 (47)
- Lactulose studies (n=8): Bresci et al, 1993 (48), Elkington et al, 1969 (49), Heredia et al, 1988 (50), Loguerico et al, 1995 (51), Poo et al, 2006 (52) , Raza et al, 2004 (53), Sharma et al, 2009 (54), Takuma et al, 2010 (55)

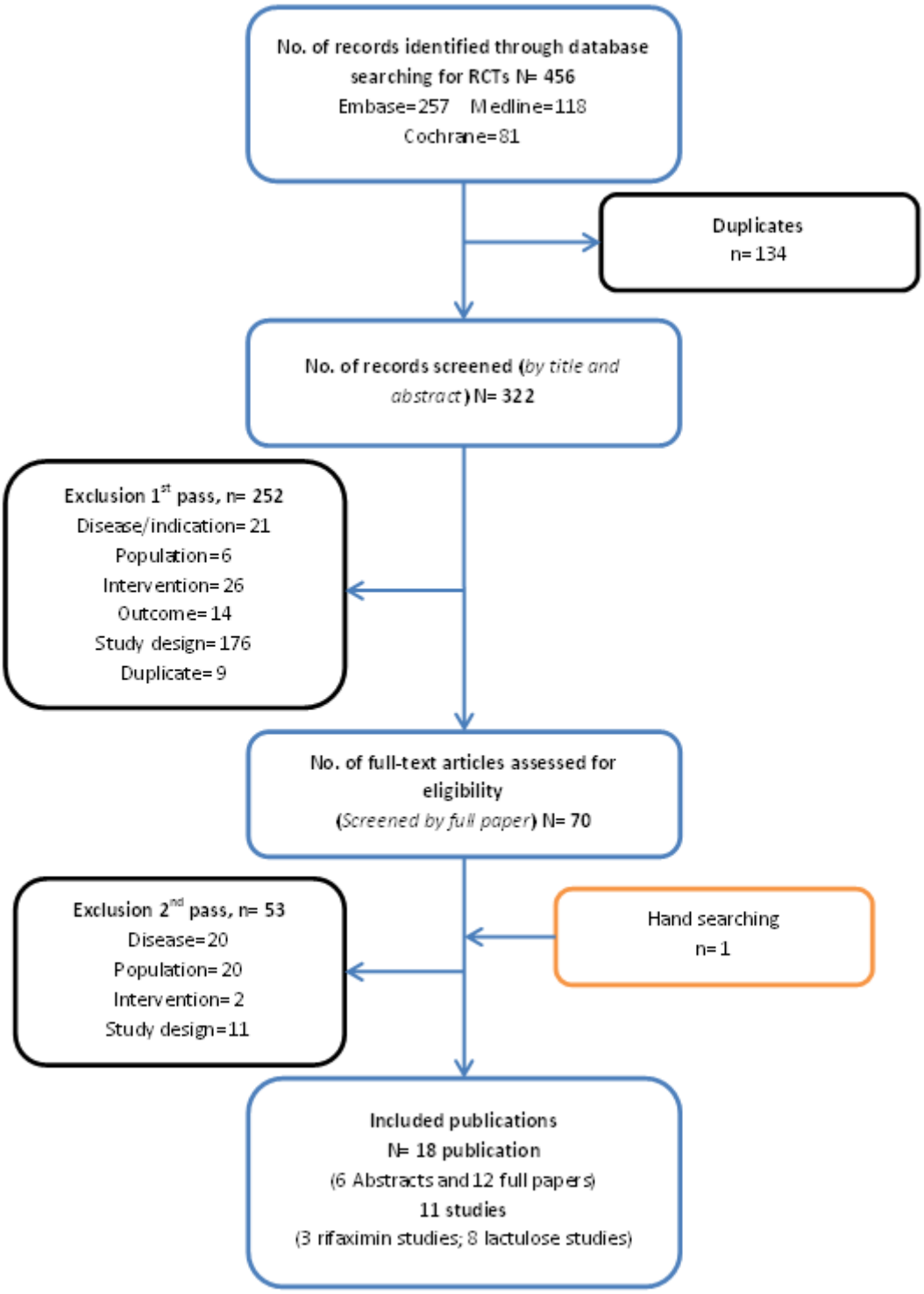
There were no relevant neomycin studies that met the final inclusion criteria.

Of the three final included rifaximin studies, two are further excluded from this submission Loguerico et al, 2003 (46) and Paik et al. 2005 (47). Loguerico et al, 2003 (46) involved pulsed/cyclical treatment with rifaximin at a different dose/regimen to the UK licensed indication for rifaximin. Paik et al. 2005 (47) involved treatment with rifaximin at a different dose/regimen to the UK licensed indication for rifaximin in a Korean population.

None of the lactulose studies identified are reported in any further detail in this submission. In the rifaximin pivotal study (Bass et al, 2010) 91% of patients received concomitant lactulose.

The systematic review schematic is shown in Figure 2.

Figure 2: Schematic for the systematic review of clinical evidence



6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Pivotal Phase III Study (RFHE3001)

One pivotal Phase III RCT (RFHE3001) for rifaximin was identified in the systematic review as relevant to this submission and is described in full within. The main sources of information for this study are:

- Bass *et al*. Rifaximin treatment in HE (22).
- The Clinical Study Report (CSR) for study RFHE3001 (27).

Open-label Phase III Study (RFHE3002)

A separate review of the unpublished data from the manufacturer database was also undertaken to identify any relevant unpublished data in the population of interest (i.e. adults who have had prior acute episodes of HE). One further study was identified, an open-label Phase III study (RFHE3002) which provides long-term evaluation of the safety and tolerability of rifaximin (45). Patient who successfully completed the pivotal Phase III RCT (RFHE3001) were eligible to participate in study RFHE3002 in addition to new patients. Further information on RFHE3002 is provided in the list of relevant non-RCTs (Section 6.8). The CSR for RFHE3002 is the main source of information for this submission (45).

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

The systematic review of clinical evidence identified one RCT of rifaximin in the population of interest to this submission (Table 4).

Table 4: List of relevant RCTs

Study no.	Intervention	Comparator	Population	Objective	Primary study ref
RFHE3001; Phase III, multi-centre, 6-month, randomised, double-blind, placebo-controlled study.	Rifaximin 550 mg taken orally BID†.	Placebo matching 550 mg rifaximin tablets taken orally BID†.	Patients currently in remission from previously demonstrated, overt, episodic HE associated with chronic liver disease.	**Primary objective:** Compare the maintenance of remission from previously demonstrated recurrent, episodic HE during 6 months of treatment. **Secondary objective:** Compare the safety, tolerability, and QoL.	Bass *et al*, 2010 (22) CSR (27).

Abbreviations: BID, twice a day; HE, hepatic encephalopathy; QoL, quality of life; CSR, clinical study report
† Patients had the option to use lactulose as concomitant medication during the study, if the patient was receiving lactulose therapy at baseline. In the rifaximin and placebo groups, 91.4% and 91.2% of patients, took concomitant lactulose during the course of the study, respectively.

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

The pivotal Phase III RCT study (RFHE3001) compares rifaximin with placebo. Patients had the option to use lactulose as concomitant medication during the study, if the patient was receiving lactulose therapy at baseline. In the rifaximin and placebo groups, 91.4% and 91.2% of patients took concomitant lactulose during the course of the study, respectively.

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

No identified studies above were excluded from further discussion.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in Section 6.8 and key details should be presented in a table; the following is a suggested format.

One non-RCT relevant to the decision problem is summarised in Table 5.

Table 5: List of relevant non-RCTs

Study no.	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
RFHE3002; Open-label, multi-centre study (≥ 24 months).	Rifaximin 550 mg taken orally BID for ≥ 24 months.	All eligible patients had a history of HE, a Conn score of 0 to 2 at enrolment, and either had successfully participated in study RFHE3001, or were new patients enrolled with ≥ 1 verifiable episode of HE within 12 months prior to screening.	**Primary objective:** to evaluate the long-term safety and tolerability of rifaximin treatment (550 mg BID) in patients with a history of HE.	CSR (45)	Long-term data on safety and tolerability of rifaximin.

Abbreviations: BID, twice a day; HE, hepatic encephalopathy; CSR, clinical study report

6.3 Summary of methodology of relevant RCTs

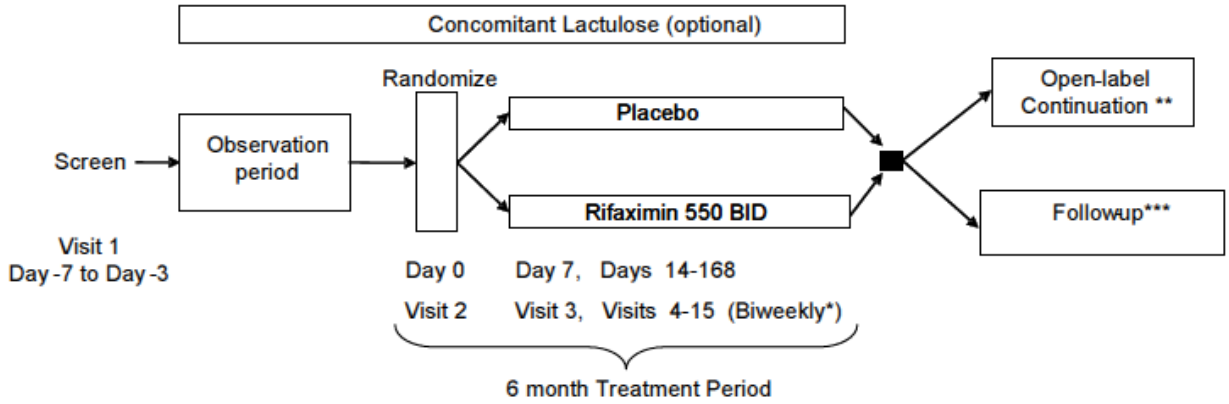
6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this Section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following table provides a suggested format for when there is more than one RCT.

Study Design: Pivotal Phase III Study (RFHE3001)

A Phase III, international (United States, Canada and Russia) multicentre, randomised, double-blind, placebo-controlled study conducted over a 6-month period. The study was designed to evaluate the efficacy and safety of rifaximin (550 mg twice daily [BID]) compared with placebo (placebo [BID]), in patients who were in remission from recurrent, overt, episodic hepatic encephalopathy (HE) resulting from chronic liver disease. The study design schematic is provided in Figure 3.

Figure 3: Study design



* Visits 6, 8, 10, 12, & 14 on Days 42, 70, 98, 126, and 154 are optional

** Subjects who experienced a breakthrough overt HE episode or who completed 6 months of therapy were eligible for enrolment in continuation study RFHE3002.

*** Subjects who terminated early for reasons other than breakthrough overt HE were contacted at 6 months from randomisation to determine if subjects had experienced a breakthrough overt HE episode or other outcome (i.e. mortality status). Subjects who did not enrol in the open-label continuation study within 16 days of the end-of study/early termination visit completed a follow-up visit (Day 182±2).

Randomisation

Patients were randomly assigned on Day 0 (Visit 2) to receive rifaximin 550 mg BID or placebo BID in a 1:1 ratio.

Blinding

Patients, investigators and other personnel participating in the trial were blinded to the study treatments by their identical appearance and labelling. The investigator was permitted to unblind a patient's treatment assignment only in an emergency, when knowledge of the study drug was essential for the clinical management or welfare of the patient.

Interventions and comparators

Patients were randomised to receive one of the following interventions for 6 months or until patients discontinued treatment because of a breakthrough episode of HE or other reason:

- Rifaximin (n=140, randomised)
  - Rifaximin 550 mg tablets taken orally BID
- Placebo (n=159, randomised)
  - Placebo matching 550 mg rifaximin tablets taken orally BID for 6 months.

Treatment compliance was determined by counting the numbers of tablets in the bottles of study drug that were returned to the site by the patient.

Permitted and disallowed concomitant medications

Lactulose use was optional during the study, if patients were already receiving lactulose at baseline. Lactulose was available to patients throughout the study. Lactulose was to be titrated to an appropriate dose during the 3- to 7-day Observation Period according to accepted medical practice. Lactulose therapy was not to be initiated after baseline (Day 0, Visit 2) unless the patient was withdrawn from the study. Patients were not to

start lactulose use during the Observation Period unless the investigator believed there was an immediate need for this therapy. If the patient was receiving lactulose at baseline, then dose modifications (i.e. reductions, increases, stopping and restarting lactulose therapy) were permitted as needed.

Other permitted medications included:

- If used prior to screening: antidepressants, methadone, prescription and non-prescription sleep aids and antihistamines
- Diuretics
- Laxatives or stool softeners
- If used for a minimum of 2 months prior to screening and dose expected to remain stable throughout study: Neurontin® (gabapentin) and Lyrica® (pregabalin)

Use of any of the following medications was prohibited:

- Benzodiazepines or drugs with benzodiazepine effect
- Any experimental drug
- Non-absorbable disaccharides, except lactulose
- Psyllium-containing intestinal regulators (e.g. Metamucil®)
- Narcotics, psychotropics, and other psychoactive and neuroactive agents, except as described above
- Warfarin-type anticoagulants
- Elemental zinc (multi-vitamins with zinc were allowed), sodium benzoate, milk thistle, s-adenosylmethionine
- Rifampin
- Alternative, herbal, or complementary therapies for HE other than those required to manage fluid and electrolyte homeostasis
- Antibiotic therapy with any of the following: metronidazole, oral vancomycin, oral neomycin, any known nephrotoxic agent (e.g. aminoglycosides); and non-systemic or systemic antibiotic, except as allowed in exclusion criterion 11
- Branched-chain amino acids and l-ornithine-l-aspartate

Patients were to stop the use of prohibited medications beginning at the screening visit, with the exceptions of rifaximin (self-administered outside of the study) and neomycin, which were to be discontinued at the time of randomisation and for the duration of treatment with the study drug.

Discontinuation of study therapy

During the study, a patient may have been removed from treatment by the investigator for the following reasons:

- Patient experienced an adverse event (AE), which, in the judgment of the investigator, represented an unacceptable risk to the patient
- Patient developed any condition fulfilling the exclusion criteria

- Patient experienced a breakthrough overt HE episode
- Patient became pregnant
- Patient requested to be withdrawn

Patients who had a breakthrough overt HE episode[5] had the option to roll-over to the open-label continuation study. The investigator was allowed to discontinue individual patients at any time during the study. Patients were encouraged to complete the study; however, they could voluntarily withdraw at any time. The investigator was required to provide written documentation of the reason for discontinuation on the case report form (CRF). Regardless of the reason for withdrawal, all patients were asked to undergo an end-of-treatment evaluation and a follow-up evaluation at 2 weeks post treatment. Any patients withdrawn prior to randomisation were not replaced.

Patients who terminated early for reasons other than breakthrough overt HE were contacted at 6 months from randomisation to determine if they had experienced a breakthrough overt HE episode or other outcome (i.e. death). Therefore, complete capture was achieved for breakthrough overt HE episodes up to 6 months post randomisation.

Assessments

Assessments were conducted in the Screening/Observation Period (Visit 1, Day -7 to -3), during the treatment period up to and including End-of-Study (EOS) Period (Visit 2 to 15, Day 0 ±1 to 168 ±2) and in the Follow-Up Period (Visit 16, Day 182 ±2). Assessments were conducted as in-clinic treatment visits on Days 7 and 14, and every 2 weeks thereafter until Day 168. Visits on Days 42, 70, 98, 126 and 154 were optional, if patients did not attend an in-clinic visit on these days, they were assessed by telephone (±2 days).

Assessments included the Conn score, asterixis grade, venous ammonia concentrations, Critical Flicker Frequency (CFF) score, the occurrences of HE-related serious AEs (SAEs) leading to hospitalisation, the occurrence of spontaneous bacterial peritonitis (SBP), Chronic Liver Disease Questionnaire (CLDQ) scores, and other quality of life (QoL) measurements (Epworth Sleepiness Scale [ESS] scores and Short-Form 36 [SF-36] questionnaire scores).

Duration of follow-up

Patients who experienced a breakthrough overt HE episode, or who completed 6 months of therapy, were eligible for enrolment in the open-label study (RFHE3002). As the EOS visit was considered to be the screening visit for the open-label study, any patients enrolled in study RFHE3002 were not followed-up further in study RFHE3001.

[5] Defined as an increase in Conn score to ≥ 2, or an increase in Conn score and asterixis grade of 1 each for those patients who entered the study with a Conn score of 0.

Patients who did not enrol in the open-label study within 16 days of the EOS/early termination visit completed a Follow-up visit (Day 182 ±2).

Participants: Pivotal Phase III Study (RFHE3001)

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

The inclusion and exclusion criteria for the pivotal study RFHE3001 were as follows:

Inclusion Criteria

Patients were eligible for inclusion in the study if they met all of the following criteria:

- Male or female aged 18 years or older
- Women of non-childbearing potential or who were practicing adequate birth control, as determined by the investigator
- Conn score of 0 or 1 (the Conn score can range from 0 to 4, with higher scores indicating more severe impairment)
- Documented recurrent, overt HE i.e. ≥ 2 episodes of overt HE associated with cirrhosis or portal hypertension equivalent to a Conn score ≥ 2 within 6 months prior to screening. At least 1 episode must have been verifiable by medical records from a treating physician/clinic/hospital. An episode of HE was defined as an increase in Conn score from 0 or 1 to ≥ 2, followed by a decrease to 0 or 1. HE episodes primarily attributable to gastrointestinal haemorrhage requiring ≥ 2 units of blood by transfusion, medications, renal failure requiring dialysis, or CNS insult such as a subdural haematoma were not counted for inclusion
- Patient had a Model End Stage Liver Disease (MELD) score of ≤ 25 (the MELD score can range from 6 to 40, higher scores indicating more severe disease)
- If the patient had a history of portal-systemic shunt, TIPS placement or revision must have been performed >3 months prior to screening
- Patient had to have close family or other personal contacts acting as close observers during the conduct of the trial
- A IRB/IEC-approved consent form was signed prior to any study related activities

Exclusion Criteria

Patients were excluded from the study for any of the following:

- A significant medical or psychiatric condition which, in the opinion of the investigator, precluded participation in the study
- Patient was expected to receive a liver transplant within 1 month of screening
- A history of intolerance to lactulose and patient was unwilling to discontinue lactulose use during the study
- A history of allergy to rifampin or rifaximin

- Participation in an investigational drug or device study within 30 days prior to study screening
- Patient was pregnant or at risk of pregnancy, or was breastfeeding
- Patient had consumed an alcoholic beverage within 14 days of screening or showed evidence of drug dependence
- A diagnosis of HIV
- A history of tuberculosis infection or treatment for a tuberculosis infection. If the patient had a previous positive test for tuberculosis antigen then they must have had a current negative chest x-ray to be eligible
- A diagnosis of chronic renal and/or respiratory insufficiency or inter-current infections
- Active SBP or patient required daily prophylactic antibiotic therapy. Patients who required concomitant antibiotic therapy with a once per week dosing regimen were eligible to participate if they had started their therapy at least 1 month prior to screening
- Patient had been treated with sedatives within 7 days prior to screening
- Presence of intestinal obstruction or inflammatory bowel disease
- A visual impairment disorder (e.g. glaucoma, diabetic retinopathy, or macular degeneration) or a neurological disease beyond HE that could have impacted performance on neuropsychological assessments and psychometric tests
- Active malignancy within the last 5 years, except basal cell carcinoma of the skin, or if female, in situ cervical carcinoma that had been surgically excised
- Any condition or circumstance that would have prevented completion of the study or interfered with analysis of study results, including history of non-compliance with treatments or visits
- Ongoing gastrointestinal (GI) bleeding or a GI haemorrhage of sufficient severity to require hospitalisation and a transfusion of ≥ 2 units of blood within 3 months prior to screening
- Renal insufficiency defined as serum creatinine of >2.0 mg/dL.
- Anaemia, as defined by a haemoglobin level of <8 mg/dL.
- Significant hypovolemia, or any electrolyte abnormality that could have affected mental function (e.g. serum sodium <125 mEq/L, serum calcium >10 mg/dL).
- Severe hypokalemia as defined by a potassium level <2.5 mEq/L.

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

The patient baseline demographic characteristics for the intention-to-treat (ITT) population in the pivotal study, RFHE3001, are summarised in Table 8. The median age of patients was 56 (ranging from 21 to 82) with 19.4% of patients being over the age of 65. Most patients were white (86%) and male (60.9%). The relative distributions of

patients by demographic characteristics were comparable between treatment groups in the ITT population.

Table 6: Patient demographics: Study RFHE3001 (ITT population)

Baseline demographic characteristics	rifaximin (N=140)	Placebo (N=159)	Total (N=299)
Age (years)			
Mean (SD)	55.5 (9.6)	56.8 (9.2)	56.2 (9.4)
Median (range)	55.0 (26 – 82)	57.0 (21 – 78)	56.0 (21 – 82)
Age distribution, n (%)			
<65	113 (80.7)	128 (80.5)	241 (80.6)
≥ 65	27 (19.3)	31 (19.5)	58 (19.4)
Male gender, n (%)	75 (53.6)	107 (67.3)	182 (60.9)
Race, n (%)			
American Indian/Alaskan native	5 (3.6)	3 (1.9)	8 (2.7)
Asian	4 (2.9)	8 (5.0)	12 (4.0)
Black or of African ancestry	7 (5.0)	5 (3.1)	12 (4.0)
Native Hawaiian/Pacific islander	2 (1.4)	1 (0.6)	3 (1.0)
White	118 (84.3)	139 (87.4)	257 (86.0)
Other	3 (2.1)	3 (1.9)	6 (2.0)
Missing data	1 (0.7)	0	1 (0.3)
Country, n (%)			
United States	93 (66.4)	112 (70.4)	205 (68.6)
Canada	8 (5.7)	6 (3.8)	14 (4.7)
Russia	39 (27.9)	41 (25.8)	80 (26.8)

Abbreviations: SD, standard deviation.

The baseline characteristics of the underlying disease, HE, were generally comparable across treatment groups (Table 7). Baseline Conn score and asterixis grade were 0 for the majority of patients (66.9% and 68.2%, respectively). The mean time since the most recent verified HE event was 71.1 (±49.62) days, and most patients had 2 (69.6%) or 3 (21.4%) HE episodes during the 6-month period prior to study entry. The Conn score for the most recent HE episode prior to study entry was 2 for 81.9% of patients.

Table 7: Hepatic Encephalopathy baseline characteristics of participants in RFHE3001

HE baseline characteristics	Rifaximin (N=140)	Placebo (N=159)	Total (N=299)
Time since first diagnosis of HE† (months)			
n	139	159	298
Mean (SD)	20.8 (23.1)	21.9 (26.4)	21.4 (24.9)
Number of HE episodes within the past 6 months, n (%)			
2	97 (69.3)	111 (69.8)	208 (69.6)
3	29 (20.7)	35 (22.0)	64 (21.4)
4	5 (3.6)	8 (5.0)	13 (4.3)
5	7 (5.0)	1 (0.6)	8 (2.7)
≥6	2 (1.4)	3 (1.9)	5 (1.6)
Missing	0	1 (0.6)	1 (0.3)
Duration of verified current remission‡, (days)			
N	139	158	297
Mean (SD)	68.8 (47.7)	73.1 (51.3)	71.1 (49.6)
Conn score during most recent HE episode prior to study, n (%)			
Grade 1	1 (0.7)	2 (1.3)	3 (1.0)
Grade 2	115 (82.1)	130 (81.8)	245 (81.9)
Grade 3	20 (14.3)	24 (15.1)	44 (14.7)
Grade 4	3 (2.1)	2 (1.3)	5 (1.7)
Missing	1 (0.7)	1 (0.6)	2 (0.7)
Conn score at baseline, n (%)			
Grade 0	93 (66.4)	107 (67.3)	200 (66.9)
Grade 1	47 (33.6)	52 (32.7)	99 (33.1)
Asterixis grade, n (%)			
Grade 0	96 (68.6)	108 (67.9)	204 (68.2)
Grade 1	41 (29.3)	45 (28.3)	86 (28.8)
Grade 2	2 (1.4)	5 (3.1)	7 (2.3)
Grade 3	1 (0.7)	1 (0.6)	2 (0.7)

Abbreviations: HE, hepatic encephalopathy; SD, Standard deviation.
†Defined as first dose date of study drug – date of first diagnosis of HE +1. ‡Defined as date of first dose of study drug – date of most recent verified, qualifying HE episode before first dose +1.

The mean (±SD) duration of treatment was 130.3 (±56.5) days in the rifaximin group and 105.7 (±62.7) days in the placebo group. The rate of compliance, defined as use of at least 80% of dispensed tablets, was high in both study groups (84.3% in the rifaximin group and 84.9% in the placebo group).

A total of 273 of 299 patients (91.3%) received lactulose as a prior medication and as a concomitant medication during the study (Table 8). The percentages of patients who took lactulose were similar between the rifaximin (91.4%) and placebo (91.2%) groups during the course of the study. Three patients (1 on rifaximin and 2 on placebo) were not

receiving lactulose before the study and started lactulose use during the treatment period. The mean daily doses of lactulose during the study period were stable (Table 8).

Table 8: Concomitant lactulose therapy: Study RFHE3001 (ITT Population)

	Rifaximin (N=140)	Placebo (N=159)	Total (N=299)
Prior lactulose use – n (%)			
Yes	128 (91.4)	145 (91.2)	273 (91.3)
No	12 (8.6)	14 (8.8)	26 (8.7)
Lactulose use during the treatment period – n (%)			
Yes	128 (91.4)	145 (91.2)	273 (91.3)
No	12 (8.6)	14 (8.8)	26 (8.7)
Newly initiated lactulose use – n (%) (started lactulose during the treatment period)			
Yes	1 (0.7)	2 (1.3)	3 (1.0)
No	139 (99.3)	157 (98.7)	296 (99.0)
Mean (±SD) lactulose used/day, cups†	3.14 (±2.096)	3.51 (±2.592)	–
Mean rate of change in lactulose use (±SD), cups†/day	0.0030 (±0.03767)	0.0076 (±0.10595)	–

†1 cup of lactulose is 10 g in 15 mL

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL) and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

Outcomes: Pivotal Phase III Study (RFHE3001)

Primary outcome

The primary outcome was the time to the first breakthrough overt HE episode (from the first dose of study drug). An overt HE episode was defined as an increase in the Conn score to ≥2, (i.e. 0 or 1 to ≥2) or an increase in Conn and asterixis score of 1 grade each for those patients who entered the study with a Conn score of 0. At the baseline assessment, patients were in remission (Conn score of 0 or 1).

The Conn score (also known as the West Haven score) detects the severity of impaired mental status in overt HE according to four progressive stages (0 to 4, with higher scores indicating more severe impairment):

- 0 = no personality of behavioural abnormality

- 1 = trivial lack of awareness, euphoria or anxiety, shortened attention span, or impaired ability to add or subtract subtraction
- 2 = lethargy, temporal disorientation, obvious personality change, or inappropriate behaviour
- 3 = somnolence or semistupor, with responsiveness to stimuli; confusion, gross disorientation, bizarre behaviour
- 4 = coma

The asterixis grade detects worsening neurological impairment according to the flapping tremor. Asterixis was determined by the patient extending their arms with wrists flexed backwards and fingers open for 30 seconds or more. The asterixis grades are:

- 0 = no tremors
- 1 = few flapping motions
- 2 = occasional flapping motions
- 3 = frequent flapping motions
- 4 = almost continuous flapping motions

Key secondary outcomes

The five key secondary outcomes assessed in the study were as follows:

- Time to first HE-related hospitalisation
- 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 Chronic Liver Disease Questionnaire (CLDQ) at end of treatment
- Mean change from baseline in venous ammonia concentration at end of treatment

Other secondary efficacy endpoints

- Time to diagnosis of SBP
- Mean change from baseline in CFF values at each post-baseline assessment and at end of treatment
- The numbers and proportions of patients in each level of change from baseline in Conn scores at each post-baseline assessment and at end of treatment.
- The numbers and proportions of patients in each level of change from baseline in asterixis grades at each post-baseline assessment and at end of treatment.

Tertiary efficacy endpoints

- Mean change from baseline in Epworth Sleepiness Scale (ESS) total score at each post-baseline assessment and at end of treatment.
- Proportion of patients who had an ESS total score ≥10 at each post-baseline assessment and at end of treatment

- Mean change from baseline in SF-36 QoL scores at each post-baseline assessment and at end of treatment
- Average daily lactulose usage (cup/day, 1 cup = 15 mL)

Statistical analysis and definition of study groups: Pivotal Phase III study (RFHE3001)

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Population datasets analysed

The study populations used in the analyses were as follows:

- The ITT population, which included all randomised patients who received at least one dose of study drug
- The safety population, which included all randomised patients who received at least one dose of study drug and provided at least 1 post-baseline safety assessment

Hypothesis under investigation and power calculation

The null hypothesis of interest is: H_0: $\beta_{rifaximin} = 0$

Versus the alternative: H_A: $\beta_{rifaximin} \neq 0$, where $\beta_{rifaximin}$ is the coefficient of the treatment arm (rifaximin) in a Cox proportional hazards regression model compared with the placebo group. Thus, $\beta_{rifaximin}$ represents the log of the hazard ratio for comparing rifaximin with placebo and is equivalent to testing that the hazard ratio for the occurrence of an HE breakthrough overt event is significantly different from 1.

A total of 250 patients, approximately 125 each in the rifaximin and placebo groups, were planned for enrolment in the study. This sample size is based on an analysis of the relative risk of experiencing a breakthrough overt HE event using Cox regression analysis of time to first breakthrough overt HE episode.

Sample-size calculations were based on an assumption of breakthrough episodes of HE occurring in 50% and 70% of patients receiving rifaximin and placebo, respectively which would result in a hazard ratio for rifaximin relative to placebo of approximately 0.58 (coefficient of the treatment arm [$\beta_{rifaximin}$] = -0.54) for time to first breakthrough overt HE episode. On the basis of these assumptions, sample size calculations show that approximately 100 evaluable patients per treatment group would provide >80% power to demonstrate that rifaximin was superior to placebo.

The Cox proportional-hazards model was used, with a 2-sided test and a significance level of 0.05, to compare the time to a breakthrough episode between the rifaximin group

and the placebo group (after adjustment for geographic region). Kaplan–Meier methods were used to estimate the proportions of patients having a breakthrough episode at successive time points during the study. Patients who withdrew from the study early for reasons other than the development of HE (e.g. another adverse event or the patient's request) were contacted 6 months after randomisation to determine whether a breakthrough episode of HE had occurred since withdrawal. Data for patients who did not have breakthrough HE before Day 168 were censored at the time of last contact or on Day 168, whichever was earlier. Data for patients who did not have a hospitalisation involving HE before Day 168 were censored at the time of study termination or on Day 168, whichever was earlier. The same statistical methods were used to analyse the key secondary end point: time to the first hospitalisation involving HE.

The five key secondary endpoints (Section 6.3.5) were analysed in a hierarchical fashion. Significance tests were conducted for all secondary efficacy endpoints. Results of significance testing were reported in hierarchical order, from endpoint number 1 through to endpoint number 5, until a non-significant p-value was found ($p>0.05$). After finding a non-significant p-value, all significance tests of subsequent endpoints were considered exploratory in nature.

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Pre-planned subgroup analyses

The primary efficacy endpoint was evaluated in subgroups of patients according to the following characteristics: geographic region, sex, age, race or ethnic group, baseline MELD score, baseline Conn score, diabetes at baseline, duration of current verified remission, number of episodes of HE within the 6-month period before randomisation, lactulose use at baseline, and previous placement of a transjugular intrahepatic portosystemic shunt.

Subgroup data for modelling

Pre-planned subgroup analyses were not conducted on the following populations within the trial, but were undertaken as subgroup analyses in the economic model:

a) Subgroup A- All patients in both arms received concomitant lactulose use (i.e. 91.3% of the ITT population [rifaximin n=128, placebo n=145])

b) Subgroup B – None of the patients in both arms received concomitant lactulose use (i.e. 8.7% of the ITT population [rifaximin n=12, placebo n=14]).

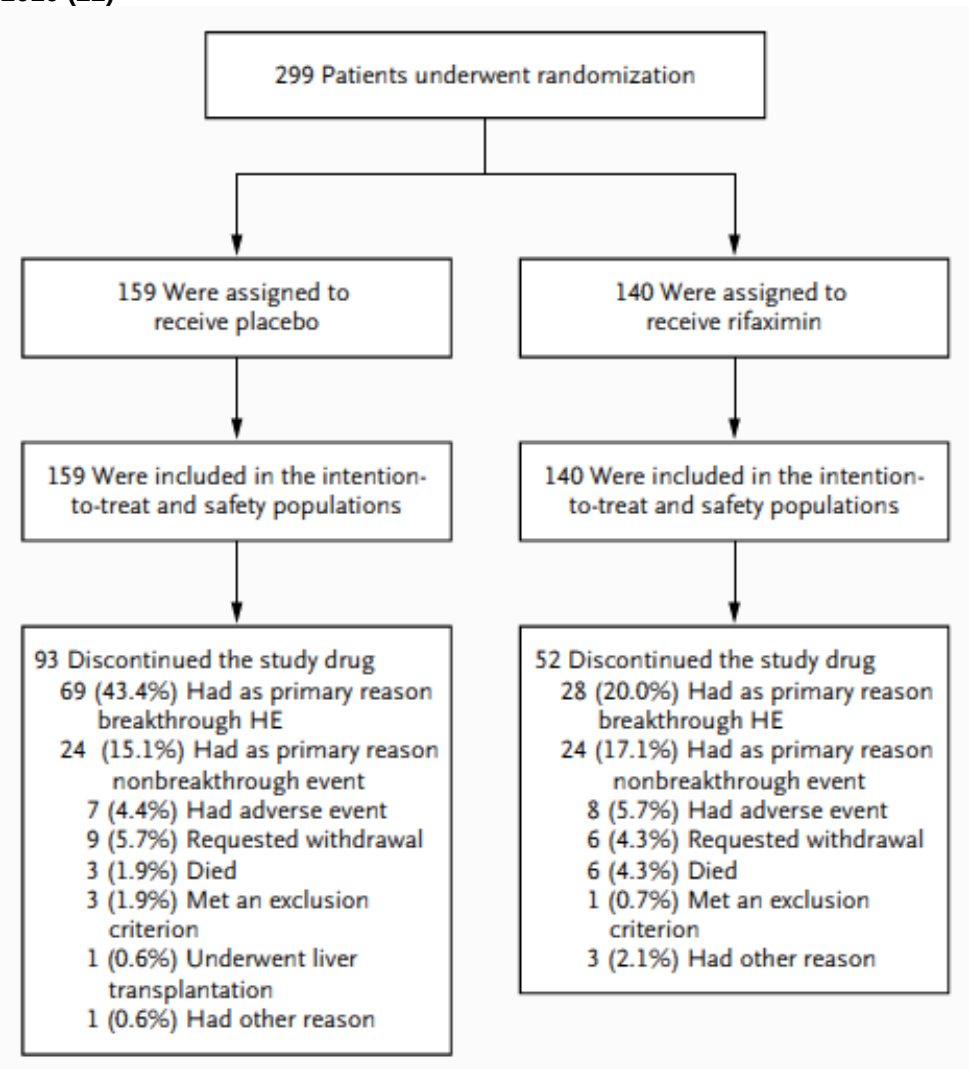
Patient level data were therefore used to allow presentation of the cost effectiveness of rifaximin within these subgroups (see details in the economic section).

Participant flow: Pivotal Phase III Study (RFHE3001)

6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

A CONSORT flow chart showing the numbers of patients who were eligible to enter the pivotal study, and who were randomised and allocated to each treatment are presented in Figure 4. All randomised patients received at least 1 dose of study drug. A total of 251 (84%; 116 [rifaximin], 135 [placebo]) patients completed the study as per protocol.

Figure 4: Randomisation and follow-up of the ITT population; illustration from Bass et al., 2010 (22)



Abbreviation: HE, Hepatic encephalopathy

6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See Section 10.3, appendix 3 for a suggested format.

A complete quality assessment for each RCT is provided in Section 10.3.

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one RCT, tabulate the responses.

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan-Meier plots.

6.5.3 For each outcome for each included RCT, the following information should be provided.

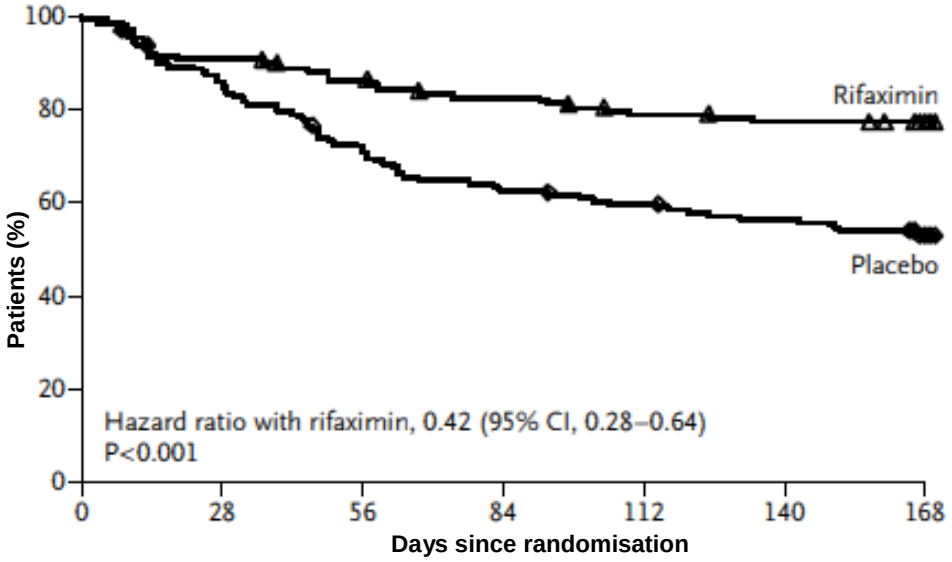
- ***The unit of measurement.***
- ***The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio in an equivalent statistic. Both absolute and relative data should be presented.***
- ***A 95% confidence interval.***
- ***Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.***
- ***When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.***
- ***Other relevant data that may assist in the interpretation of the results may be included, such as adherence to medication and/or study protocol.***
- ***Discuss and justify definitions of any clinically important differences.***
- ***Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.***

6.5.4 Results: pivotal Phase III study (RFHE3001)

Primary efficacy outcome: Time to first breakthrough overt HE episode

Breakthrough overt HE episodes were reported in 31 of 140 patients in the rifaximin group (22.1%) and 73 of 159 patients in the placebo group (45.9%). Figure 5 shows the time to a breakthrough episode. The hazard ratio for the risk of a breakthrough episode in the rifaximin group compared with the placebo group, was 0.42 (95% confidence interval [CI], 0.28 to 0.64; p<0.001), reflecting a relative reduction in the risk of a breakthrough episode by 58% with rifaximin compared with placebo during the 6-month study period. These data suggest that four patients would need to be treated with rifaximin for 6 months to prevent one overt HE episode. The degree to which rifaximin reduced the risk of a breakthrough episode was consistent across the 12 subgroups examined (Figure 5).

Figure 5: Kaplan-Meier estimates of the primary end point in the ITT population by study group; illustration from Bass et al., 2010 (22)



Abbreviations: CI confidence interval, HE hepatic encephalopathy.
Symbols represent patients for whom data were censored. The p-values were calculated using the log-rank test, with stratification by geographic region.

Because patients who did not experience a breakthrough overt HE episode were followed after study discontinuation, the primary efficacy endpoint was analysed up to last contact. Results were similar to the analysis of the 6-month treatment period. A total of 34 of 140 patients in the rifaximin group and 73 of 159 patients in the placebo group had a breakthrough overt HE episode during the treatment period plus follow-up; the hazard ratio was 0.461 (95% CI: 0.307 to 0.693; p<0.0001).

Covariate analyses

To investigate the potential effect of prognostic factors on breakthrough overt HE episode, a log rank test stratified on each covariate was performed: sex, age, race, geographical region, MELD score, Conn score, diabetes, duration of current verified remission, and HE episodes in the 6 months prior to randomisation. Prior lactulose use was not analysed as a covariate because >90% of subjects in each treatment group

were receiving lactulose prior to study entry. Of the analysed prognostic factors, the following were found to be strong independent predictors of breakthrough overt HE episodes:

- Age (p=0.0160)
- MELD score (p=0.0003)
- Duration of current verified remission (p=0.1089)
- Number of prior HE episodes (p=0.0022)

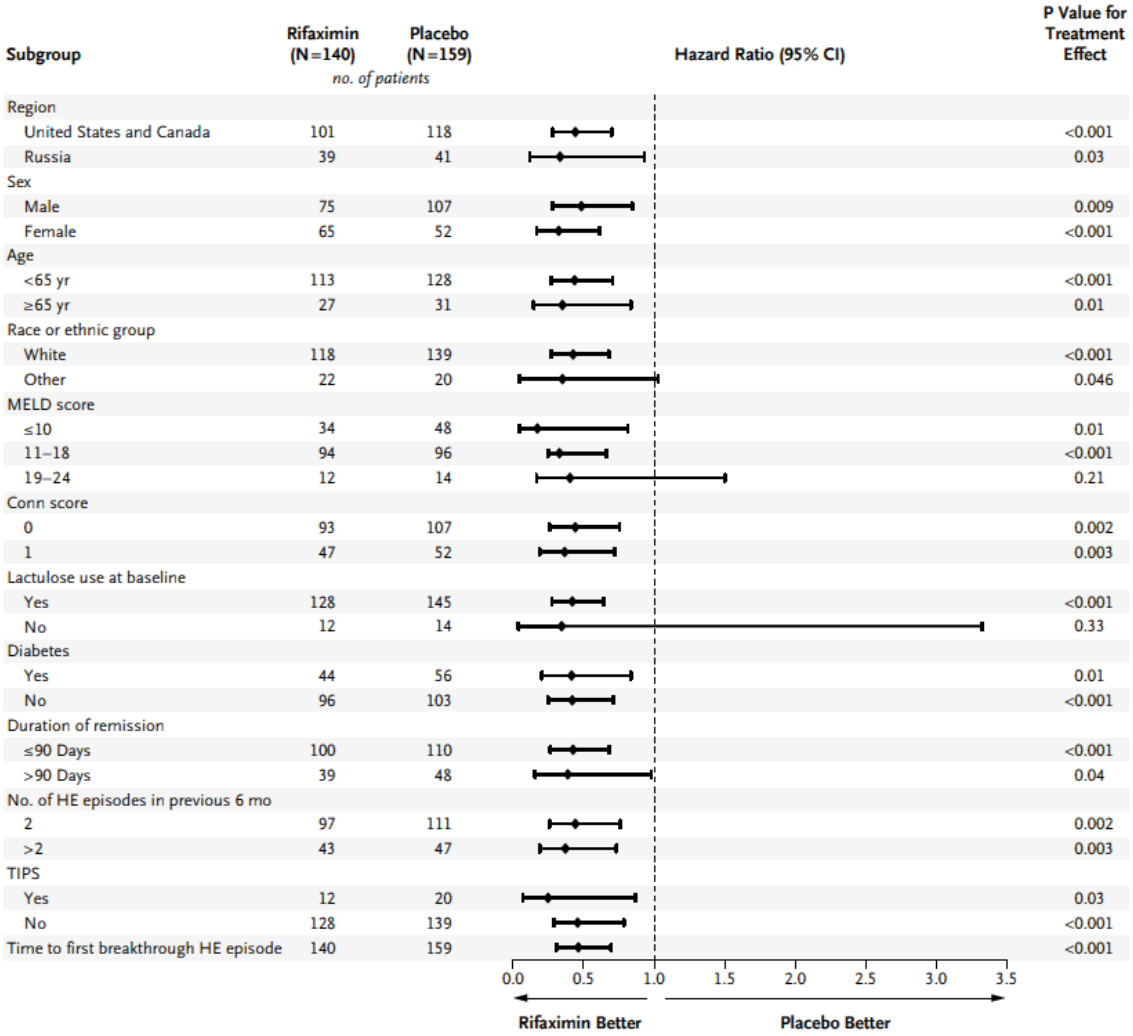
To control for these factors on outcome due to chance imbalances between treatment groups, multivariate analysis was performed using the Cox proportional hazards model. The hazard ratio (rifaximin to placebo) was 0.403 (95% CI: 0.264 to 0.617) (p<0.0001). Thus, rifaximin treatment, after adjusting for significant prognostic factors, resulted in a 60% reduction in the risk of experiencing a breakthrough overt HE episode during the course of this study (compared with placebo). The most influential prognostic factors in the multivariate analysis were age (p=0.0225) and baseline MELD score (p=0.0005).

The results indicate that the highly significant protective effect of rifaximin (p<0.0001) against breakthrough overt HE episodes was maintained in the presence of statistically significant competing factors.

Sub-group analyses of the primary efficacy outcome

Subgroup analyses were conducted to determine the robustness and precision of the rifaximin treatment effect for the primary efficacy endpoint. Outcomes for the primary efficacy endpoint were evaluated in the following subgroups: geographic analysis region (North America vs Russia), sex, age (<65 vs ≥ 65 years), race (white vs non-white), baseline MELD level (≤ 10, 11 – 18, 19 – 24), baseline Conn score (0 vs 1), prior lactulose use (yes vs no), diabetes at baseline (yes vs no), duration of current verified remission (≤ 90 days vs >90 days), and the number of HE episodes within the 6 months prior to randomisation (2 vs >2). The effect of rifaximin treatment in reducing the risk of experiencing breakthrough overt HE episodes during the 6-month treatment period was consistent across all subgroups (Figure 6).

Figure 6: Results of the subgroup analysis: Study RFHE3001; illustration from Bass et al., 2010 (22)



Abbreviations: HE, hepatic encephalopathy; TIPS, transjugular intrahepatic portosystemic shunt.
Hazard ratios for the risk of a breakthrough episode of HE during the 6-month study period are shown for the rifaximin group, as compared with the placebo group, for various subgroups. The MELD score can range from 6 to 40, with higher scores indicating more severe disease. The Conn score can range from 0 to 4, with higher scores indicating more severe impairment. The p-values were calculated by means of the log-rank test. Race or ethnic group was self-reported.

Sensitivity analyses

Overt episodic HE is marked by single or recurrent episodes of neuropsychiatric impairment usually precipitated by specific conditions or risk factors (i.e. comorbid conditions). Because patients who had ongoing comorbid conditions (i.e. known precipitating factors for HE episodes) at the time of randomisation may have been unstable, a sensitivity analysis of the primary efficacy endpoint was carried out, where these patients were excluded from the analysis. Ongoing comorbid conditions included analgesic use, constipation, infection, and portal shunt surgery. Rifaximin treatment resulted in significant reductions in the risk of breakthrough overt HE in patients with or without comorbidities. Hazard ratios of rifaximin to placebo were 0.248 (95% CI: 0.108 to 0.571) (p=0.0004) in patients who had comorbid conditions and 0.512 (95% CI: 0.313 to 0.839) (p=0.0068) in patients without comorbid conditions. Because patients who took

concomitant medications, indicated for the treatment or prevention of HE, may have influenced the effect of rifaximin on the outcome of the primary endpoint, a second sensitivity analysis was performed whereby patients satisfying the above condition were excluded from the ITT population. Rifaximin treatment also resulted in a significant reduction in the risk of breakthrough overt HE when patients who received concomitant medications were excluded from the analysis; hazard ratio of rifaximin to placebo was 0.419 (95% CI: 0.275 to 0.640) ($p<0.0001$).

Subgroup data for modelling

Data were taken from RFHE3001 on the time to first breakthrough overt HE episode in the population where all patients in both arms have concomitant lactulose use (Subgroup A, 91.3% of the ITT population) and no patients have concomitant lactulose use (Subgroup B, 8.7% of the ITT population) in order to model these subgroups.

Kaplan-Meier plots of the primary endpoint in these subgroups are presented in **Error! Reference source not found.** and **Error! Reference source not found.**.

[redacted]

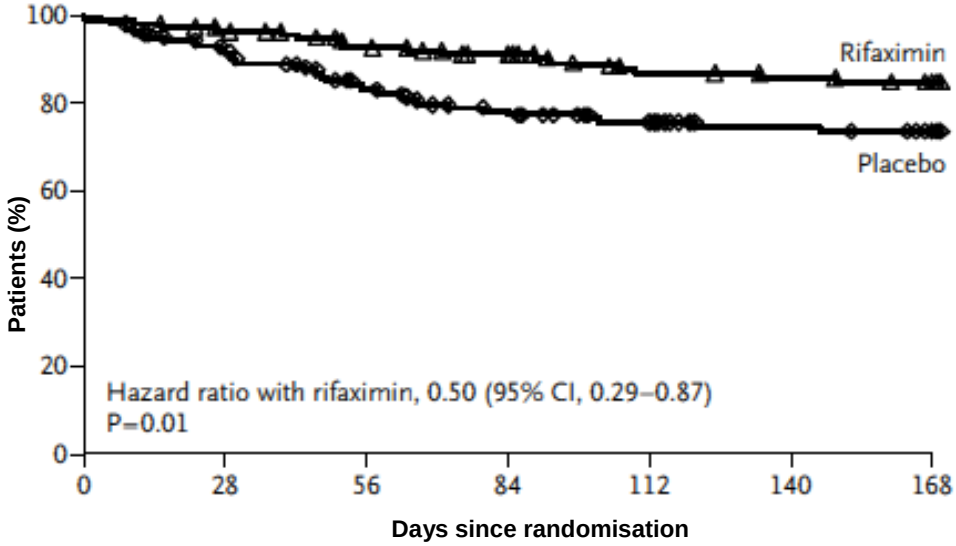
[redacted]

[redacted]

Key secondary endpoints

Time to first HE-related hospitalisation: Hospitalisation involving HE was reported for 19 of 140 patients in the rifaximin group (13.6%) and 36 of 159 patients in the placebo group (22.6%). The hazard ratio for the risk of such hospitalisation in the rifaximin group, as compared with the placebo group, was 0.50 (95% CI, 0.29 to 0.87; p=0.01), reflecting a reduction in the risk by 50% with rifaximin as compared with placebo (Figure 7). Thus, nine patients would need to be treated with rifaximin for 6 months to prevent one hospitalisation involving HE.

Figure 7: Kaplan-Meier estimate of time to first HE-related hospitalisation (ITT population): Study RFHE3001; illustration from Bass et al., 2010 (22)



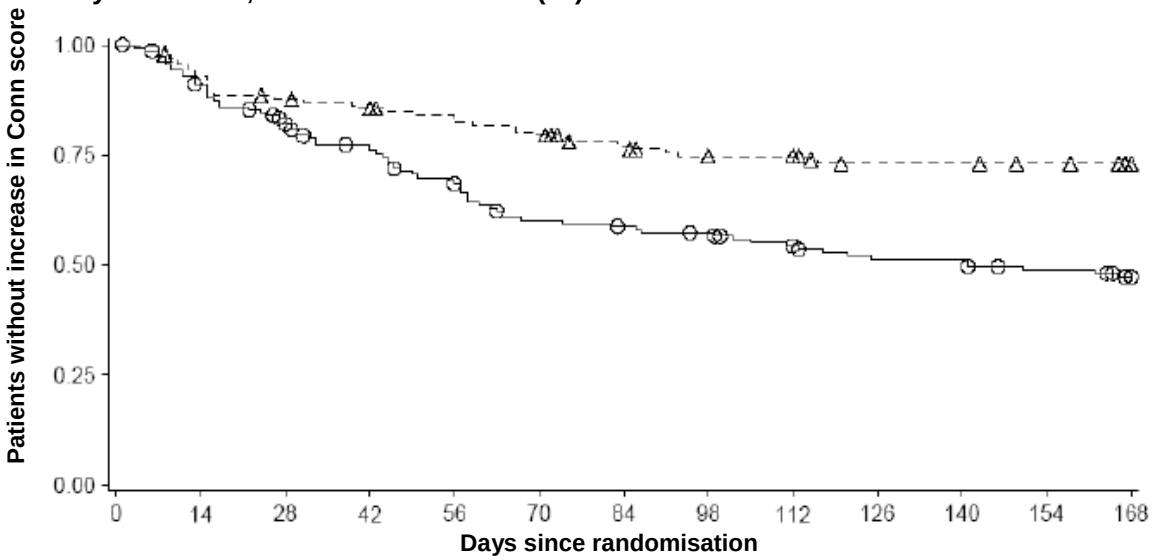
Abbreviations: CI, confidence interval; HE, hepatic encephalopathy.
Symbols represent patients for whom data were censored. The p values were calculated by means of the log-rank test, with stratification according to geographic region. CI denotes confidence interval, and HE hepatic encephalopathy.

Time to any increase from baseline in Conn score: Figure 8 illustrates time to any increase from baseline in Conn score by treatment group in the ITT population.

Patients who discontinued prior to experiencing an increase in Conn score and prior to completion of the 6-month treatment period were censored at the time of discontinuation.

By evaluating the time to any increase from baseline in Conn score, it was possible to compare the earliest worsening in mental status between patients in the rifaximin and placebo treatment groups, even if the worsening did not reach the definition of breakthrough HE (e.g. increase in Conn score from 0 to 1). Increases in Conn score were reported for 37 of 140 patients and 77 of 159 patients in the rifaximin and placebo groups, respectively. A highly significant protective effect of rifaximin was observed; hazard ratio in the rifaximin group relative to placebo was 0.463 (95% CI: 0.312 to 0.685) ($p<0.0001$) for the risk of experiencing an increase in Conn score (i.e. worsening in mental status) during the 6-month treatment period.

Figure 8: Kaplan-Meier estimate of time to first increase in Conn score (ITT population): Study RFHE3001; illustration from CSR (27)

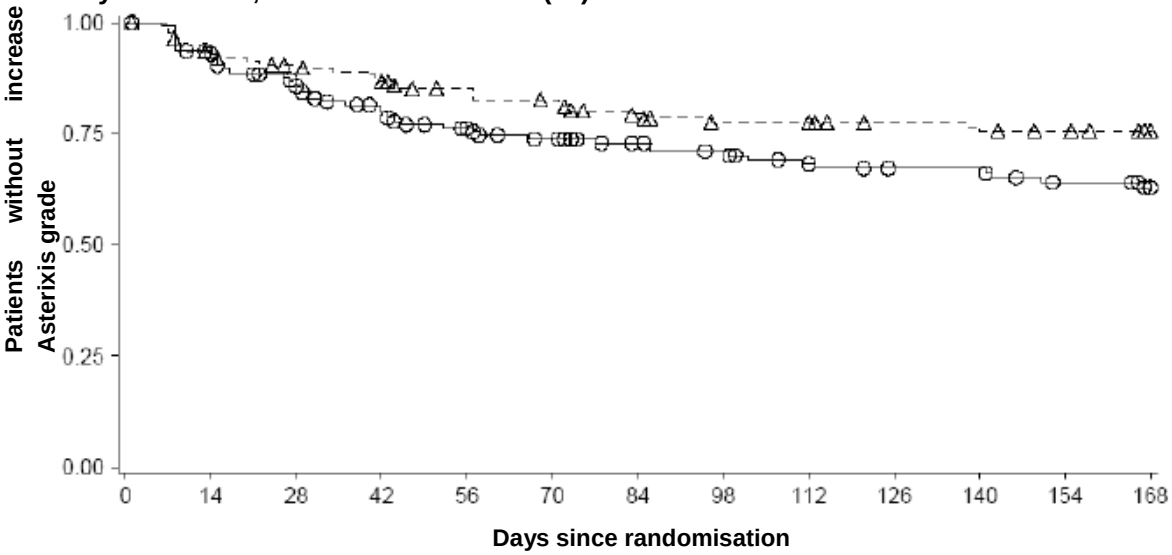


Dashed line: rifaximin; solid line: placebo. Open circles and triangles: censored subjects. Subjects who discontinued prior to the first increase in Conn score and prior to completion of the 6-month treatment period were censored at the time of discontinuation.

Time to any increase from baseline in asterixis grade: Figure 9 illustrates time to any increase from baseline in asterixis grade by treatment group in the ITT population. Patients who discontinued prior to experiencing an increase in asterixis grade and prior to completion of the 6-month treatment period were censored at the time of discontinuation.

By evaluating the time to any increase from baseline in asterixis grade, it was possible to compare the earliest worsening in neuromotor functioning between patients in the rifaximin and placebo treatment groups. Increases in asterixis grade were reported for 32 of 140 patients and 50 of 159 patients in the rifaximin and placebo groups, respectively. A protective effect of rifaximin against an increase in asterixis grade (i.e. worsening in neuromotor functioning) was observed that showed a trend toward statistical significance. The hazard ratio in the rifaximin group relative to placebo was 0.646 (95% CI: 0.414 to 1.008) (p=0.0523) for the risk of experiencing an increase in asterixis grade during the 6-month treatment period.

Figure 9: Kaplan-Meier estimate of time to first increase in asterixis grade (ITT population): Study RFHE3001; illustration from CSR (27)



Abbreviations: CI, confidence interval, HE, hepatic encephalopathy.
Symbols represent patients for whom data were censored. The p-values were calculated by means of the log-rank test, with stratification according to geographic region.

Mean change from baseline in fatigue domain score on the CLDQ at end of treatment: Patients ranked their level of fatigue by using a 7-point scale from the worst response (1, high degree of fatigue) the best response (7, minimal fatigue). Minimal differences between placebo and rifaximin groups were observed in the changes from baseline in CLDQ fatigue scores. Mean (SD) fatigue scores were 3.28 (±1.326) vs 3.34 (±1.406) at baseline and 3.57 (±1.527) vs 3.51 (±1.529) in the rifaximin and placebo groups, respectively. It is important to note that, because of altered mental and neuromotor status, it was not possible for patients to complete the CLDQ assessment during an overt HE breakthrough episode. Therefore, as mental status was closer to baseline levels at the time of end of treatment assessments, CLDQ results may have been similar to baseline levels for patients who had breakthrough overt HE episodes.

Mean change from baseline in venous ammonia concentration at each post baseline assessment and at end of treatment: Venous ammonia levels were highly variable over the course of the study. However, patients in the rifaximin group had greater reductions in venous ammonia levels compared with placebo-treated patients, and this between-group difference showed a statistical trend in favour of the rifaximin group (p=0.0818).

Table 9: Mean (SD) changes from baseline in venous ammonia level by treatment group (ITT population): Study RFHE3001

µg/dL	Rifaximin N=140	Placebo N=159	p-value†
Baseline	n=132	n=149	
Mean (SD) venous ammonia level	87.9 (47.76)	92.1 (55.24)	
End of treatment	n=132	n=141	
Mean (SD) venous ammonia level	83.9 (45.02)	88.4 (45.75)	
Change from baseline to and of treatment	n=125	n=131	
Mean (SD) change in venous ammonia level	-5.7 (46.77)	-0.3 (58.13)	p=0.0818

Baseline value was the last available value prior to first dose of study drug, and end of treatment value was the last available post-baseline value during the treatment period.
†p-value was calculated using analysis of covariance with effects for treatment and geographic analysis region, and baseline as a covariate.

Other secondary efficacy endpoints

The results of other secondary and tertiary efficacy endpoints are summarised in Table 10. Conn score, asterixis and CFF results significantly favoured rifaximin over placebo. There were no significant differences between the treatment groups regarding any of the other outcomes (SBP was not evaluable). There were no consistent differences between the placebo and rifaximin groups in change from baseline in CLDQ, ESS or SF-36.

However, it is important to note that in a post-hoc analysis of the pivotal study, in which the Chronic Liver Disease Questionnaire (CLDQ) was administered to a sub-population of 219 patients from the USA and Canada:

- Significant differences in health-related QoL (HRQoL) were seen in patients experiencing breakthrough HE episodes, compared with those who remained in remission, as determined by time-weighted average Chronic Liver Disease Questionnaire (CLDQ) scores (10).

- Higher HRQoL scores were noted across all domains in the group of patients in remission from HE episodes (10).

- Across all domains there were significant improvements in the HRQOL* of patients who were in remission in the rifaximin 550 mg BID group (n=75) compared with those in the placebo group (n=59) (10).

*As determined by differences in least square means of time-weighted average CLDQ scores.

Table 10: [redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Critical flicker frequency				
n Change, mean Δ (SD)	139 0.945 (4.75)	155 0.355 (4.70)	–	0.0320
Spontaneous bacterial peritonitis				
Too few patients (n=2 with rifaximin; n=5 with placebo) experienced SBP to compare time to onset of SBP.				

Abbreviations: CI, confidence interval, HE, hepatic encephalopathy; OR, odds ratio.
Baseline value was the last available value prior to first dose of study drug, and end of treatment value was the assessment at breakthrough overt HE episode for subjects who had breakthrough HE and the last available post baseline value for subjects without breakthrough HE during the treatment period.
†p-value was calculated using proportional odds model with effects for treatment and geographic analysis region

6.6 Meta-analysis

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- ***Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.***
- ***Statistically combine (pool) the results for the both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).***
- ***Provide an adequate description of the methods of statistical combination and justify their choice.***
- ***Undertake sensitivity analysis when appropriate.***
- ***Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).***

6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

A meta-analysis was inappropriate because only one RCT and one single-arm non-RCT are available relevant to the decision problem.

6.6.3 If any of the relevant RCTs listed in response to Section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

N/A

6.7 Indirect and mixed treatment comparisons

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in Section 10.4, appendix 4.

No studies were identified in the systematic review (see section 6.1 and 6.2) that would allow a comparison of rifaximin with neomycin alone or neomycin with lactulose.

Whilst an attempt was made to identify studies for such a comparison the following should be noted:

- In the UK neomycin is licenced for hepatic coma but it is not licenced for the reduction in recurrence of episodes of overt HE.

- The SPC for neomycin carries the following warnings relating to hepatic impairment and to long-term use (21), which Norgine considers make it inappropriate as a comparator in long-term treatment for the prevention of HE recurrences:

    - Impaired hepatic function or auditory function, bacteraemia, fever, and possibly exposure to loud noises have been reported to increase the risk of ototoxicity, while volume depletion or hypotension, liver disease, or female sex have been reported as additional risk factors for nephrotoxicity.

    - When used as an adjunct in the management of hepatic coma, care should be taken that administration is of the minimal period necessary, since prolonged exposure to the drug may result in malabsorption.

    - Since prolonged therapy may result in the overgrowth of non-sensitive organisms, treatment should not be continued longer than necessary to prevent superinfection due to the overgrowth of non-sensitive organisms.

- There are currently no clinical data to support the use of neomycin in the reduction of recurrence of HE in patients ≥ 18 years of age (see section 6.2). No controlled trials with neomycin have demonstrated equal or superior efficacy to lactulose in the patient population of interest in this submission.

- There is no clinical data in the literature to support the use of neomycin in combination with lactulose and this is a new addition to the comparator section of the final scope.

- Neomycin would appear not to be routinely used in clinical practice in the prevention of recurrence of in patients in remission. Based on neomycin usage in Primary Care in England in 2011 (as sourced from Prescription Cost Analysis via the NHS Information Centre) there were only 29 prescriptions of Neomycin Tablets 500mg issued in the year 2011, and 2,320 tablets used. Furthermore, as the data source

does not specify an indication we believe that this usage is likely to be across a number of different indications. Norgine considers that overall neomycin usage is minimal and it should therefore not be included as a comparator. This was confirmed by advisory board members.

Neomycin and neomycin with lactulose is therefore not considered by Norgine to be a comparator and during consultation had requested neomycin to be removed from the final scope.

6.7.2 Please follow the instructions specified in Sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in Section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

N/A

6.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

N/A

6.7.4 For the selected trials, provide a summary of the data used in the analysis.

N/A

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

N/A

6.7.6 Please present the results of the analysis.

N/A

6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

N/A

6.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

N/A

6.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

N/A

6.8 Non-RCT evidence

6.8.1 If non-RCT evidence is considered (see Section 6.2.7), please repeat the instructions specified in Sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in Sections 10.6 and 10.7, appendices 6 and 7.

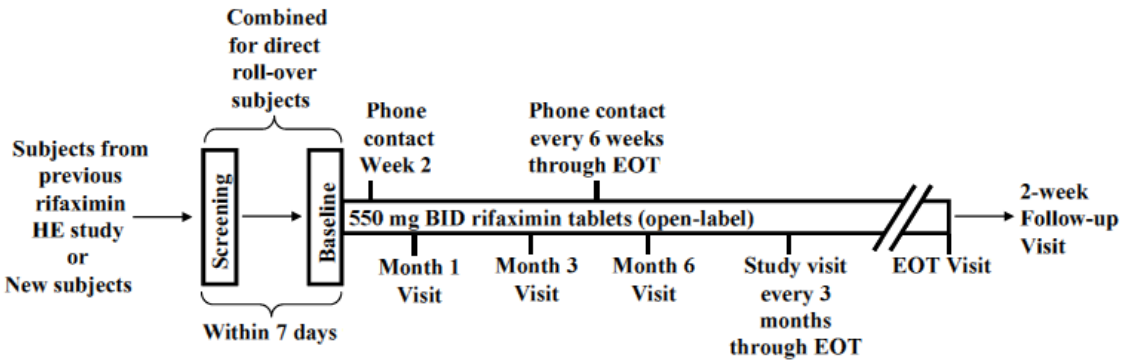
There is one non-RCT (study RFHE3001) relevant to this submission, listed in Table 5 in Section 6.2.7. The methodology and results for this non-RCT (study RFHE3002) are presented below.

A critical appraisal of study RFHE3001 can be found in Section 10.7.

Study Design: Open-label study (RFHE3002)

RFHE3002 was a Phase III, international (United States, Canada and Russia), multicentre, open-label study. The primary objective of the study was to evaluate the long-term safety and tolerability of rifaximin 550 mg BID in approximately 500 patients with a history of HE (45). Treatment in the study was planned to continue for at least 24 months on an outpatient basis, or until regulatory approval of rifaximin for reduction in risk of overt HE recurrence, or until the sponsor closed the study, whichever came first. The study design is shown in Figure 10. Interim results from this study have been presented as abstracts to international hepatic congresses (23, 62), but no peer review publications were available at the time of writing.

Figure 10: Study design: RFHE3002



Randomisation and blinding

Study RFHE3002 was single-arm and open-label.

Intervention

Rifaximin 550 mg, taken orally BID and self-administered by patients on an out-patient basis. Patients were instructed to take one rifaximin 550 mg tablet BID, approximately every 12 hours (total daily dose of 1100 mg rifaximin). No concurrent treatment control was used.

Prior and concomitant therapy

All concomitant drugs were recorded in the subject‘s notes and the CRF, stating the medication name, the indication, and the duration of treatment. If possible, concomitant medications were maintained at stable doses during the study. For subjects who participated in a previous rifaximin HE study, all medications taken upon enrolment and at any time during this study were recorded in the subject‘s notes and CRF, even if the start date for these medications was before or during the previous rifaximin study. Any experimental drugs and narcotics were prohibited during the study (stable doses of methadone were allowed if deemed appropriate by the investigator).

Discontinuation of study therapy

The conditions for study discontinuations were the same as those for study RFHE3001, described in Section 6.3.2, with the following exception:

Patients who experienced an episode of recurrent HE (defined as an increase of Conn score to ≥ 2, an increase in Conn and asterixis score of 1 grade each for those patients who entered the study with a Conn score of 0, or an increase in Conn score to ≥ 3 for patients who had a Conn score of 2 at study entry) during the study were not automatically withdrawn, but could continue on open-label medication unless withdrawal was requested by the patient or the investigator.

Assessments

Study visits were scheduled at Screening, Baseline, Month 1, Month 3, and every 3 months thereafter until the End-of-Treatment (EOT) visit. An End-of-Study (EOS) follow-up visit was scheduled for 2 weeks after the EOT. At the investigator‘s discretion, Screening and Baseline evaluations for the study were combined for patients rolling over ≤ 30 days after their last dose of study drug in the RFHE3001 study. The EOT visit for RFHE3001 could also be considered as the Screening/Baseline visit for this open-label study. In addition to clinic visits, telephone contacts were planned for Week 2 and every 6 weeks after Month 3 until EOS.

Duration of follow-up

Treatment in the RFHE3002 study was planned to continue for at least 24 months on an outpatient basis, or until regulatory approval of rifaximin for reduction in risk of overt HE recurrence, or until the sponsor closed the study, whichever occurred first.

Participants

All eligible patients had a history of HE, a Conn score of 0 to 2 at enrolment, and either successfully participated in the previous HE study with rifaximin (RFHE3001), or were new patients enrolled with ≥ 1 verifiable episode of HE within 12 months prior to screening. Patients who had participated in RFHE3001 and had experienced a HE episode or associated symptoms were only eligible for this study if the investigator and patient did not perceive study medication as a possible cause of the HE episode/symptoms.

Inclusion and exclusion criteria were otherwise those already described in Section 6.3.3 for study RFHE3001.

[redacted]

Most patients had baseline Conn scores of either 0 (66%) or 1 (30%) and asterixis grades of 0 (71%) or 1 (24%). The time since the most recent verified HE event was substantially shorter in the new rifaximin group compared with the continuing rifaximin group (**Error! Reference source not found.**). New and continuing patients were also different with respect to the number of HE episodes experienced prior to screening for RFHE3002.

The difference between new and continuing rifaximin patients in duration of remission from HE was due to the fact that most continuing rifaximin patients (60 of 70) had maintained remission for the duration of RFHE3001 (6 months) and most new rifaximin patients had recent HE events prior to entry in RFHE3002. The difference between new and continuing rifaximin patients in number of prior HE episodes during the 12 months prior to screening for RFHE3002 was due to differences in entry requirements for RFHE3001 and RFHE3002: Two episodes of HE (Conn score ≥ 2) within 6 months prior to screening were required for inclusion in RFHE3001 and ≥ 1 episode of HE (Conn score ≥ 2) within 12 months of screening was required for RFHE3002.

[redacted]

Statistical analysis and definition of study groups: Study RFHE3002

Population datasets analysed

All analyses were performed for the Safety population which included all subjects who entered the open-label study who received at least one dose of open-label study medication and provided at least one post-baseline safety assessment.

Data is also presented for the “new rifaximin” group, which includes subjects who received placebo in RFHE3001 and rolled over into RFHE3002, as well as new subjects who did not participate in RFHE3001. The “continuing rifaximin” group includes subjects who received rifaximin in RFHE3001 and rolled over into RFHE3002.

Power calculation

The primary objective of this study was to gather long-term safety information on subjects with a history of HE. Therefore, the sample size was established based on the number of subjects expected to be available, resulting in an anticipated enrolment for this open-label study of up to 500 subjects.

Participant flow: Study RFHE3002

XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

[redacted]

Figure 11 shows the patient flow through study RFHE3002. A total of 322 patients were enrolled at 57 study sites. Of these patients, 152 (47%) rolled over from the double-blind study (RFHE3001; 82 placebo patients and 70 patients continuing rifaximin) and 170 (53%) were new patients entered into RFHE3002. A total of 154 patients (48%) completed the study. All of the 322 patients enrolled were included in the Safety population. [redacted]

[redacted]

Figure 11[redacted]

[redacted]

[redacted]

Results: Study RFHE3002

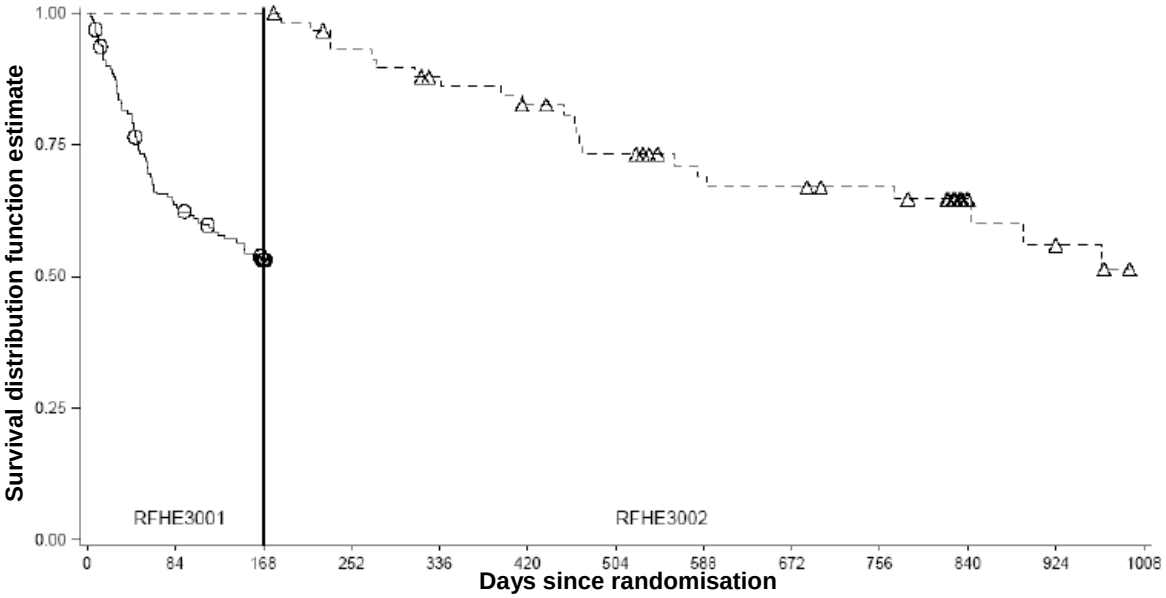
HE episodes

Treatment with rifaximin for periods longer than 6 months did not result in loss of effect regarding maintenance of remission from breakthrough overt HE episodes. The time to first breakthrough overt HE episode profiles demonstrated long-term maintenance of remission in new rifaximin patients (including placebo crossover patients from RFHE3001) and continuing rifaximin patients in RFHE3002 (i.e. rifaximin rollover patients from RFHE3001.

Rifaximin-treated patients from RFHE3001 who were in remission at the end of RFHE3001 (i.e. who did not experience a HE episode during the 6 months of treatment) were followed during open-label study RFHE3002 (n=60). [redacted]

These results demonstrate that rifaximin had a durable protective effect beginning in RFHE3001 and continuing in RFHE3002 (Figure 12).

Figure 12: Kaplan Meier estimates of distribution of time to first breakthrough HE for continuing rifaximin patients who did not have an HE episode in RFHE3001 vs placebo



Solid line: placebo in RFHE3001; broken line: continuing rifaximin; circles and triangles represent censored patients.

[redacted]

[redacted]

[redacted]

Table 11 [redacted]

[redacted]

Hospitalisations

In an analysis of the protective effect of rifaximin against hospitalisation long term, the all-cause hospitalisation rate was similar to that observed for rifaximin during the shorter double-blind trial: 0.44 events/PEY (person exposure year) in new rifaximin patients from RFHE3002 compared with 0.92 events/PEY in the rifaximin group and 1.31 events/PEY in the placebo group in RFHE3001. Similarly, the rate for hospitalisation resulting from breakthrough overt HE was 0.23 events/PEY in the new rifaximin group from RFHE3001 compared with 0.38 events/PEY in the rifaximin group and 0.78 events/PEY in the placebo group during RFHE3001.

6.9 Adverse events

Safety - Pivotal Phase III study RFHE3001

- The proportions of patients experiencing AEs, severe or serious AEs, drug-related AEs or death were comparable between the rifaximin and placebo groups
- A similar number of patients experienced drug-related SAEs, 3 with placebo and 4 with rifaximin
- Fewer patients in the rifaximin group discontinued due to AEs than in the placebo group. This difference is mostly due to a reduced incidence of HE events with rifaximin
- Deaths were predominantly due to disease progression and did not differ between the treatment groups

Safety - Open-label extension (OLE) study RFHE3002

- [redacted]
- The TEAE profile was similar to that observed in the double-blind study and TEAEs, SAEs and laboratory findings were expected based on the population of patients with chronic liver disease who were receiving lactulose therapy
- [redacted]
- [redacted]

The identification of clinical evidence is described in Sections 6.1 and 6.2. All trials relevant to this submission are listed in Table 4 in Section 0 and Table 5 in Section 6.2.7. The methodology, critical appraisal and results of relevant trials that are designed primarily to assess safety outcomes are presented in Section 6.9.1. Safety results from other studies, primarily designed to assess efficacy are described in Section 6.9.2.

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in Sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in Sections 10.8 and 10.9, appendices 8 and 9.

N/A

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

Pivotal Phase III study RFHE3001 – safety results

Because breakthrough overt HE was an efficacy outcome for the study, reported AEs (all AEs are treatment-emergent, unless otherwise stated) of HE were checked against the episodes of breakthrough overt HE. All reported AEs of HE corresponded to breakthrough overt HE episodes, with the exception of one case in one subject.

A total of 79.9% of subjects (239 of 299) experienced AEs during the course of the study, including 80% of subjects (112 of 140) in the rifaximin group and 79.9% of subjects (127 of 159) in the placebo group.

Adverse reactions in study RFHE3001 which occurred in ≥ 5% of patients receiving rifaximin and at a higher incidence than placebo are shown in Table 14.

Table 12: Adverse reactions occurring in ≥ 5% of patients receiving rifaximin and at a higher incidence than placebo in RFHE3001

MedDRA System Organ Class	Event	Placebo N=159		Rifaximin N=140	
		n	%	n	%
Blood and lymphatic system disorders	Anaemia	6	3.8	11	7.9
Gastrointestinal disorders	Ascites	15	9.4	16	11.4
	Nausea	21	13.2	20	14.3
	Abdominal pain upper	8	5.0	9	6.4
General disorders and administration site conditions	Oedema peripheral	13	8.2	21	15.0
	Pyrexia	5	3.1	9	6.4
Musculoskeletal and connective tissue disorders	Muscle spasms	11	6.9	13	9.3
	Arthralgia	4	2.5	9	6.4
Nervous system disorders	Dizziness	13	8.2	18	12.9
Psychiatric disorders	Depression	8	5.0	10	7.1
Respiratory, thoracic and mediastinal disorders	Dyspnoea	7	4.4	9	6.4
Skin and subcutaneous tissue disorders	Pruritus	10	6.3	13	9.3
	Rash	6	3.8	7	5.0

The majority of AEs were mild or moderate in severity. Severe AEs were experienced by 28.8% of subjects (86 of 299), including 26.1% in the rifaximin group and 30.8% in the placebo group. Drug-related AEs were reported for 20.7% (62 of 299) of subjects (19.3% rifaximin vs 21.4% placebo). Serious AEs were experienced by 38.1% (114 of 299) of subjects (36.4% rifaximin vs 39.6% placebo), and 25.1% (75 of 299) of subjects (21.4% rifaximin vs 28.3% placebo) had AEs resulting in study discontinuation. The percentages of subjects who had AEs, severe AEs, drug-related AEs, SAEs, AEs resulting discontinuation, and who died were similar between placebo and rifaximin groups (Table 13).

Table 13: Summary of AEs – safety population, study RFHE3001

Adverse events Number (%) patients	Placebo (N=159)	Rifaximin (N=140)	Total (N=299)
≥ 1 AE	127 (79.9)	112 (80.0)	239 (79.9)
≥ 1 drug-related AE	34 (21.4)	27 (19.3)	61 (20.4)
≥ 1 severe AE	49 (30.8)	37 (26.1)	86 (28.8)
Deaths	11 (6.9)	10 (7.1)	21 (7.0)
1 SAE	63 (39.6)	51 (36.4)	114 (38.1)
≥ 1 drug-related SAE	3 (1.9)	4 (2.9)	7 (2.3)
Discontinuation due to AEs	45 (28.3)	30 (21.4)	75 (25.1)

Abbreviations: AE, adverse event; SAE, serious adverse event

AEs were most frequently reported in the following system organ classes (SOCs; rifaximin vs placebo): GI disorders (51.4% vs 42.1%), nervous system disorders (37.9% vs 40.3%), general disorders and administration site conditions (40% vs 32.7%), infections and infestations (32.9% vs 30.8%), and respiratory, thoracic and mediastinal disorders (25.7% vs 24.5%) (Table 14). The most common AEs (rifaximin vs placebo) were: diarrhoea (10.7% vs 13.2%), nausea (14.3% vs 13.2%), peripheral oedema (15% vs 8.2%), fatigue (12.1% vs 11.3%), dizziness (12.9% vs 8.2%), ascites (11.4% vs 9.4%), and headache (10% vs 10.7%). Episodes of HE that qualified as SAEs were recorded for 12.1% of rifaximin subjects vs 21.4% of placebo subjects.

The rifaximin group had higher incidences of anaemia (7.9% with rifaximin vs 3.8% with placebo), peripheral oedema (15% vs 8.2%), pyrexia (6.4% vs 3.1%), arthralgia (6.4% vs 2.5%), and dizziness (12.9% vs 8.2%) than the placebo group. Subjects in the rifaximin group also had a higher incidence of AEs in the eye disorders SOC than subjects in the placebo group: 9.3% (13 of 140) vs 1.9% (3 of 159), respectively. No subject had an eye disorder AE that resulted in study discontinuation.

Table 14: Adverse events occurring in ≥ 2% of patients, by SOC, study RFHE3001

System organ class Adverse events, n (%)	**Placebo (N=159)**	**Rifaximin (N=140)**	**Total (N=299)**
Subjects with ≥ 1 AE	127 (79.9)	112 (80.0)	239 (79.9)
Blood and lymphatic system disorders	**8 (5.0)**	**15 (10.7)**	**23 (7.7)**
Anaemia	6 (3.8)	11 (7.9)	17 (5.7)
Gastrointestinal disorders	**67 (42.1)**	**72 (51.4)**	**139 (46.5)**
Nausea	21 (13.2)	20 (14.3)	41 (13.7)
Diarrhoea	21 (13.2)	15 (10.7)	36 (12.0)
Ascites	15 (9.4)	16 (11.4)	31 (10.4)
Abdominal pain	13 (8.2)	12 (8.6)	25 (8.4)
Vomiting	14 (8.8)	10 (7.1)	24 (8.0)
Abdominal distension	12 (7.5)	11 (7.9)	23 (7.7)
Constipation	10 (6.3)	9 (6.4)	19 (6.4)
Abdominal pain upper	8 (5.0)	9 (6.4)	17 (5.7)
Flatulence	6 (3.8)	3 (2.1)	9 (3.0)
Dry mouth	3 (1.9)	4 (2.9)	7 (2.3)
Oesophageal varices haemorrhage	2 (1.3)	4 (2.9)	6 (2.0)
Abdominal pain lower	2 (1.3)	3 (2.1)	5 (1.7)
Abdominal tenderness	2 (1.3)	3 (2.1)	5 (1.7)
Stomach discomfort	1 (0.6)	3 (2.1)	4 (1.3)
General disorders and administration site conditions	**52 (32.7)**	**56 (40.0)**	**108 (36.1)**
Fatigue	18 (11.3)	17 (12.1)	35 (11.7)
Oedema peripheral	13 (8.2)	21 (15.0)	34 (11.4)
Asthenia	12 (7.5)	4 (2.9)	16 (5.4)
Pyrexia	5 (3.1)	9 (6.4)	14 (4.7)
Oedema	6 (3.8)	3 (2.1)	9 (3.0)
Pain	3 (1.9)	4 (2.9)	7 (2.3)
Chest pain	2 (1.3)	3 (2.1)	5 (1.7)
Generalized oedema	2 (1.3)	3 (2.1)	5 (1.7)
Hepatobiliary disorders	**14 (8.8)**	**11 (7.9)**	**25 (8.4)**
Jaundice	7 (4.4)	5 (3.6)	12 (4.0)
Hepatic cirrhosis	6 (3.8)	3 (2.1)	9 (3.0)
Infections and infestations	**49 (30.8)**	**46 (32.9)**	**95 (31.8)**
Urinary tract infection	14 (8.8)	8 (5.7)	22 (7.4)
Cellulitis	3 (1.9)	3 (2.1)	6 (2.0)
Upper respiratory tract infection	3 (1.9)	3 (2.1)	6 (2.0)
Pneumonia	1 (0.6)	4 (2.9)	5 (1.7)
Rhinitis	1 (0.6)	3 (2.1)	4 (1.3)
Injury, poisoning, and procedural complications	**16 (10.1)**	**16 (11.4)**	**32 (10.7)**
Contusion	3 (1.9)	5 (3.6)	8 (2.7)
Fall	1 (0.6)	3 (2.1)	4 (1.3)
Procedural pain	1 (0.6)	3 (2.1)	4 (1.3)
Investigations	19 (11.9)	13 (9.3)	32 (10.7)

System organ class Adverse events, n (%)	**Placebo (N=159)**	**Rifaximin (N=140)**	**Total (N=299)**
Weight increased	3 (1.9)	3 (2.1)	6 (2.0)
Metabolism and nutrition disorders	**21 (13.2)**	**28 (20.0)**	**49 (16.4)**
Decreased appetite	6 (3.8)	3 (2.1)	9 (3.0)
Dehydration	2 (1.3)	5 (3.6)	7 (2.3)
Hyperkalemia	2 (1.3)	5 (3.6)	7 (2.3)
Anorexia	2 (1.3)	3 (2.1)	5 (1.7)
Hyperglycaemia	2 (1.3)	3 (2.1)	5 (1.7)
Hypoglycemia	2 (1.3)	3 (2.1)	5 (1.7)
Hyponatremia	2 (1.3)	3 (2.1)	5 (1.7)
Musculoskeletal and connective tissue disorders	**32 (20.1)**	**31 (22.1)**	**63 (21.1)**
Muscle spasms	11 (6.9)	13 (9.3)	24 (8.0)
Back pain	10 (6.3)	9 (6.4)	19 (6.4)
Arthralgia	4 (2.5)	9 (6.4)	13 (4.3)
Pain in extremity	2 (1.3)	3 (2.1)	5 (1.7)
Myalgia	1 (0.6)	3 (2.1)	4 (1.3)
Nervous system disorders	**64 (40.3)**	**53 (37.9)**	**117 (39.1)**
Hepatic encephalopathy	34 (21.4)	17 (12.1)	51 (17.1)
Dizziness	13 (8.2)	18 (12.9)	31 (10.4)
Headache	17 (10.7)	14 (10.0)	31 (10.4)
Tremor	4 (2.5)	4 (2.9)	8 (2.7)
Amnesia	1 (0.6)	3 (2.1)	4 (1.3)
Memory impairment	1 (0.6)	3 (2.1)	4 (1.3)
Disturbance in attention	0	3 (2.1)	3 (1.0)
Hypoaesthesia	0	3 (2.1)	3 (1.0)
Psychiatric disorders	**29 (18.2)**	**27 (19.3)**	**56 (18.7)**
Insomnia	11 (6.9)	10 (7.1)	21 (7.0)
Depression	8 (5.0)	10 (7.1)	18 (6.0)
Anxiety	7 (4.4)	5 (3.6)	12 (4.0)
Confusional state	5 (3.1)	5 (3.6)	10 (3.3)
Respiratory, thoracic and mediastinal disorders	**39 (24.5)**	**36 (25.7)**	**75 (25.1)**
Cough	11 (6.9)	10 (7.1)	21 (7.0)
Dyspnea	7 (4.4)	9 (6.4)	16 (5.4)
Epistaxis	6 (3.8)	6 (4.3)	12 (4.0)
Pharyngolaryngeal pain	4 (2.5)	3 (2.1)	7 (2.3)
Skin and subcutaneous tissue disorders	**24 (15.1)**	**29 (20.7)**	**53 (17.7)**
Pruritus	10 (6.3)	13 (9.3)	23 (7.7)
Rash	6 (3.8)	7 (5.0)	13 (4.3)
Vascular disorders	**7 (4.4)**	**8 (5.7)**	**15 (5.0)**
Hypotension	2 (1.3)	3 (2.1)	5 (1.7)

Abbreviations: AE, adverse event; CI, confidence interval; SOC, system organ class.

Treatment-related AEs

The most common drug-related AEs (in ≥ 5% of both groups combined) were diarrhoea (3.6% rifaximin vs 6.9% placebo) and nausea (2.9% vs 7.5%). Each of the drug-related AEs included in Table 15 were experienced by lower percentages of subjects in the rifaximin group than in the placebo group, with the exceptions of muscle spasms, dizziness, and abdominal distension.

Table 15: Drug-related adverse events occurring in ≥ 2% of patients

System organ class Adverse events, n (%)	**Placebo (N=159)**	**Rifaximin (N=140)**	**Total (N=299)**
Subjects with ≥ 1 treatment-related AE	34 (21.4)	27 (19.3)	61 (20.4)
Gastrointestinal disorders	**25 (15.7)**	**17 (12.1)**	**42 (14.0))**
Nausea	12 (7.5)	4 (2.9)	16 (5.4)
Diarrhoea	11 (6.9))	5 (3.6))	16 (5.4)
Abdominal distension	2 (1.3)	3 (2.1)	5 (1.7)
General disorders and administration site conditions	**6 (3.8)**	**2 (1.4)**	**8 (2.7)**
Fatigue	4 (2.5)	1 (0.7)	5 (1.7)
Musculoskeletal and connective tissue disorders	**4 (2.5)**	**6 (4.3)**	**10 (3.3)**
Muscle spasms	2 (1.3)	5 (3.6)	7 (2.3)
Nervous system disorders	**10 (6.3))**	**8 (5.7)**	**18 (6.0)**
Headache	5 (3.1)	2 (1.4)	7 (2.3)
HE	3 (1.9)	2 (1.4)	5 (1.7)
Dizziness	2 (1.3)	3 (2.1)	5 (1.7)

Abbreviations: AE, adverse event; CI, confidence interval; HE, hepatic encephalopathy; SOC, system organ class.

Severe adverse events

The majority of AEs were mild or moderate in severity. Severe AEs were experienced by 28.8% of subjects (86 of 299): 26.1% of the rifaximin group and 30.8% of the placebo group. Severe AEs that occurred in five or more patients in the total patient group were anaemia (4 subjects on rifaximin vs 2 on placebo), ascites (4 vs 3), abdominal pain (4 vs 3), hepatic cirrhosis (1 vs 4), HE (9 vs 22), and oesophageal varices (3 vs 2).

The proportions of subjects who had severe, drug-related AEs were higher in the rifaximin (8 of 140) than in the placebo (4 of 159) group. The severe, drug-related AEs were abdominal pain, balance disorder and confusional state, dizziness, diarrhoea, clostridium colitis and HE, clostridium colitis, ascites and HE, and HE in 1 subject each in the rifaximin group, and HE (2 subjects), abdominal pain (1 subject), and nausea (1 subject) in the placebo group.

Deaths

A total of 21 subjects died during the study, 11 subjects in the placebo group and 10 subjects in the rifaximin group. Deaths were predominantly due to conditions associated with disease progression, including hepatic cirrhosis, decompensated liver cirrhosis, or hepatic failure.

Other serious adverse events

Overall, 38.1% (114 of 299) of subjects experienced an SAE (36.4% with rifaximin vs 39.6% with placebo). Serious AEs that were reported by 5 or more subjects in the combined placebo plus rifaximin group were ascites (4 subjects with rifaximin vs 4 with placebo), oesophageal varices (4 vs 2), hepatic cirrhosis (3 vs 6), cellulitis (3 vs 2), generalised oedema (3 vs 2), acute renal failure (2 vs 4), and pneumonia (4 vs 1).

A total of 50 subjects, 16 (11.4%) in the rifaximin group and 34 (21.4%) in the placebo group, had breakthrough overt HE episodes that satisfied the protocol-defined criteria for an SAE (e.g. due to hospitalisation).

Serious AEs that were considered related to study drug were reported in 4/140 subjects on rifaximin and 3/159 subjects on placebo. In the placebo group, all 3 events were HE, whereas the drug-related SAEs in the rifaximin group included two cases of HE, but also two cases of clostridium colitis, diarrhoea, pyrexia and ascites (1 case each, with 2 patients experiencing more than one event).

Discontinuations due to AEs

A total of 75 of 299 subjects (25.1% overall; 28.3% in the rifaximin group vs 21.4% with placebo) had AEs resulting in study discontinuation. Most of the AEs resulting in study discontinuation were HE events (30, 18.9% with rifaximin vs 14, 10% with placebo). Gastrointestinal AEs (2% overall, 1.9% with rifaximin vs 2.1% with placebo), infections and infestations (2% overall, 2.5% vs 1.4%) and hepatobiliary disorders (2% overall, 1.9% vs 2.1%) accounted for the remaining discontinuations due to AEs.

Adverse events of special interest

Adverse events of special interest were determined on the basis of known, potential side effects of systemic antibiotics as a drug class and prior experience with rifaximin. These special interest AEs include respiratory infections, GI-related infections, and symptoms of GI or respiratory infections.

The frequency of subjects who had special interest AEs were similar between treatment groups (24.3% for rifaximin vs 22% for placebo). Diarrhoea was the most common special interest AE (10.7% and 13.2%, rifaximin vs placebo), followed by bacterial peritonitis (1.4% vs 2.5%).

Higher proportions of rifaximin treated subjects vs placebo-treated subjects experienced pneumonia (2.9% vs 0.6%), haematochezia (1.4% vs 0.6%), and gastritis and clostridium colitis (each in 1.4% vs 0 subjects).

Laboratory parameters

Among the haematology parameters, higher incidences of shifts in the rifaximin group than in the placebo group were observed for red blood cell counts, lymphocyte counts, and neutrophil percentage. Decreases in red blood cell counts were reported for 10.2% (rifaximin) vs 7.0% (placebo) of subjects and decreases in lymphocyte counts for 12.7% vs 7.0% of subjects. Increases in neutrophil percentage were reported for 10.3% versus 7.0% of subjects.

Regarding chemistry parameters, higher incidences of shifts in the rifaximin group, when compared with the placebo group, were observed for lactate dehydrogenase levels,

17.2% (rifaximin) versus 7.0% (placebo) of subjects, and for blood alkaline phosphatase levels, 11.5% versus 5.6% of subjects.

For the urinalysis parameters, the rifaximin group had higher incidences of shifts than the placebo group for urobilinogen levels, 17.6% (rifaximin) versus 11.5% (placebo) of subjects, and for urine blood, 11.5% versus 6.5% of subjects.

There were no other notable between-group differences with regard to laboratory parameters.

Potentially clinically significant laboratory test results

The proportions of subjects who had potentially clinically significant results after the first dose of study drug (worsening from baseline) were generally similar between treatment groups. The two most frequently occurring post-baseline potentially clinically significant results were elevated international normalised ratio (>1.7) and decreased lymphocyte percentages (<13.5%).

Vital signs

Mean changes in vital signs from baseline to end-of-treatment were minimal, and there were no consistent differences between placebo and rifaximin treatment groups over the course of the study.

Open-label extension (OLE) study RFHE3002 – safety results

A summary of AEs is shown in **Error! Not a valid bookmark self-reference.**. A total of 300 subjects (93.2%) reported an AE, and 56% experienced an AE that was judged by the investigator to be severe.

The SOCs most frequently affected by AEs (percent of patients) were:

- Gastrointestinal tract (67%)
- Infections and infestations (57%)
- Nervous system (48%)
- General and administration site (45%)
- Metabolism and nutritional (41%)
- Musculoskeletal and connective tissue (35%)
- Respiratory, thoracic and mediastinal disorders (35%)
- Psychiatric (31%)
- Hepatobiliary (30%)

The incidence of AEs by SOC was similar between the new rifaximin and the continuing rifaximin subjects (Table 17).

Table 16: [redacted]

[redacted]

Table 17 [redacted]

[redacted]

[redacted]

[redacted]

Table 18:

[redacted]

[redacted]

Deaths

Overall, 67 deaths (21%) occurred during the study or within 30 days after the last dose of study drug and 8 additional subjects (2%) died more than 30 days after the last dose of study drug. None of the deaths in RFHE3002 were considered by the investigator to be related to study drug.

[redacted]

[redacted]

Table 19 includes adverse reactions observed in the placebo-controlled study RFHE3001 and long term study RFHE3002, listed by MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000), Not known (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 19:Adverse reactions listed by MedDRA system organ class and frequency category.

MedDRA System Organ Class	Common	Uncommon	Rare	Not known
Infections and infestations		Clostridial infection, urinary tract infection, candidiasis	Pneumonia, cellulitis, upper respiratory tract infections, rhinitis	
Blood and lymphatic system disorders		Anaemia		Thrombocytopenia
Metabolism and nutrition disorders		Anorexia, hyperkalaemia	Dehydration	
Psychiatric disorders	Depression	Confusional state, anxiety, hypersomnia, insomnia		

MedDRA System Organ Class	Common	Uncommon	Rare	Not known
Nervous system disorders	Dizziness, headache	Balance disorders amnesia, convulsion, attention disorders hypoesthesia, memory impairment		Anaphylactic reactions, angioedemas, hypersensitivity
Vascular disorders		Hot flush	Hypertension, hypotension	Presyncope, syncope
Respiratory, thoracic, and mediastinal disorders	Dyspnoea	Pleural effusion	Chronic obstructive pulmonary disease	
Gastrointestinal disorders	Abdominal pain upper, abdominal distension, diarrhoea, nausea, vomiting, ascites	Abdominal pain, oesophageal varices haemorrhage, dry mouth, stomach discomfort	Constipation	
Hepatobiliary disorders				Liver function tests abnormalities
Skin and subcutaneous tissue disorders	Rashes, pruritus			Dermatitis, eczema
Musculoskeletal and connective tissue disorders	Muscle spasms, arthralgia	Myalgia	Back pain	
Renal and urinary disorders		Dysuria, pollakiuria	Proteinuria,	

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem

Please refer to the summary box at the beginning of Section 6.9 for further details.

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

The efficacy of rifaximin for the reduction in recurrence of episodes of overt HE has been demonstrated in a **pivotal, Phase III, randomised controlled trial**. A total of 299 adult patients were randomised to either placebo or rifaximin for 6 months, or until the first breakthrough overt HE episode. Lactulose, currently the only available preventative measure available for overt HE episodes, was allowed as concomitant medication (~91% patients received concomitant lactulose). Comparison of Kaplan-Meier estimates of time to breakthrough overt HE between groups showed a highly significant protective

effect of rifaximin (p<0.0001). These results suggest that four patients would need to be treated with rifaximin for 6 months to prevent one overt HE episode. The primary efficacy endpoint of time to first breakthrough HE episodes was also examined across 12 subgroups: geographic analysis region, sex, age, race, baseline MELD score, baseline Conn score, prior lactulose use, diabetes at baseline, duration of current verified remission, and the number of HE episodes within the 6 months prior to randomisation. Hazard ratios for the time to first breakthrough HE episode significantly favoured rifaximin over placebo in all subgroups, with three exceptions: race non-white, MELD score between 19 and 24 (indicating more severe symptoms), and no lactulose use at baseline. In all three cases the results numerically favoured rifaximin (close to statistical significance for the non-white subgroup). Age, MELD score, duration of current verified remission and the number of prior HE episodes were found to be strong independent predictors of breakthrough overt HE episodes. Multivariate analysis, controlling for these factors, showed that the highly significant protective effect of rifaximin (p<0.0001) against breakthrough overt HE episodes was maintained in the presence of statistically significant competing factors.

As might be expected, considering the benefit of rifaximin regarding time to breakthrough HE episode, rifaximin also decreased the risk of HE-related hospitalisation by 50% (compared with placebo). Nine patients would therefore need to be treated with rifaximin for 6 months to prevent one hospitalisation involving HE. The risk of a worsening in Conn score was also significantly decreased by rifaximin, as demonstrated by a hazard ratio of 0.46 (p<0.0001) for rifaximin vs placebo. Rifaximin is also likely to reduce the risk of a worsening in asterixis grade, although this effect was not statistically significant in the pivotal clinical study (with a hazard ratio of 0.65, p=0.0523, vs placebo). There was no notable effect of rifaximin on fatigue or on venous ammonia concentrations.

The overall safety profile of rifaximin vs placebo over 6 months is favourable, with comparable numbers of patients experiencing AEs, drug-related AEs, severe or serious AEs and discontinuing due to AEs. More patients in the rifaximin group experienced anaemia (7.9% with rifaximin vs 3.8% with placebo), peripheral oedema (15% vs 8.2%), pyrexia (6.4% vs 3.1%), arthralgia (6.4% vs 2.5%), and dizziness (12.9% vs 8.2%) than the placebo group. There were also more eye disorders with rifaximin (9.3% vs 1.9%). There was no difference in mortality between the rifaximin and placebo groups, and deaths were predominantly due to conditions associated with disease progression. Serious AEs were only HE events in the placebo group, but included clostridium colitis, diarrhoea, pyrexia and ascites in the rifaximin group; the overall incidence of SAEs was however not different between the treatment groups. The incidences of pneumonia (2.9% vs 0.6%), haematochezia (1.4% vs 0.6%), and gastritis and clostridium colitis (each in 1.4% vs 0 subjects), which were deemed of special interest, were higher with rifaximin.

The 2-year **open-label extension study RFHE3002** recruited both participants from the double blind RFHE3001 study and new patients. A total of 322 patients were included and treated with rifaximin for up to 2 years. Inclusion and exclusion criteria were similar to those in the double-blind study, although patients were not necessarily discontinued upon the occurrence of an HE event. The primary objective of the RFHE3002 study was

to assess the long-term tolerability of rifaximin, although some efficacy endpoints were also measured.

[redacted]

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

The evidence for the benefit of rifaximin treatment for the reduction in recurrence of episodes of overt HE is primarily based on a large-scale, Phase III, double-blind, randomised, placebo-controlled clinical trial, RFHE3001, as well as an open-label, single-arm 24-month study RFHE3002 (which recruited both new subjects and subjects who had participated in RFHE3001).

In the clinical trials rifaximin was used at a dose of 550 mg BID, which corresponds to the licensed dose and dosing frequency for rifaximin in the UK. The patient population in the trials was chosen to resemble the patient population in clinical practice, including approximately 470 adults with prior acute episodes of HE due to cirrhosis. The clinical trials focussed on patient-relevant outcomes, which included the time to the first breakthrough overt HE episode, change in Conn score and asterixis grade, and adverse events. The trials were conducted in the US, Canada, and Russia, and the population

studied was considered acceptable to the EU regulatory authorities as sufficiently reflecting a European setting. The maintenance of the efficacy of rifaximin is demonstrated over 24 months in the open-label, single-arm study RFHE3002.

Subjects with severe disease (with MELD scores ≥ 25) were excluded from the clinical studies. However the results from the pivotal study showed a positive benefit of rifaximin for each subgroup including those of higher severity. Therefore, it is reasonable to assume the relative risks from the study apply to subgroups with higher severity according to Meld score, than those included in the study. Further data also suggests that rifaximin is effective in subjects with MELD scores ≥ 20 (70).

There is evidence to suggest that patients who experience HE face a higher mortality risk than patients without HE, the mortality risk increases further with more severe grade of HE (12, 14, 18-20). It is plausible that reducing the recurrence of HE, as is associated with rifaximin treatment, could result in improved overall survival. Mortality data from RFHE3001 were not sufficiently mature to address the impact of rifaximin on survival.

Whilst, the study population reflects patients with HE seen in common clinical settings (District General Hospitals), it doesn't provide evidence for patients at the more severe end of the disease spectrum. In the economic analysis rather than using the RCT data on mortality, data are taken from other sources ((12, 14) to reflect the whole range of patients who would present with HE in clinical practice.

Study RFHE3001 does not capture the substantial burden on carers. HE can cause patients to become confused, unable to complete simple tasks and even unable to communicate. Such patients will often require substantial help from a caregiver to ensure that they can manage to complete their daily activities (4, 11). Bajaj et al. 2011 (11) interviewed caregivers of two sets of patients with cirrhotic liver disease – those with HE and those without. Caregivers of patients with HE report a significantly higher burden than caregivers of patients without HE.

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The effectiveness of rifaximin in the reduction in recurrence of episodes of overt HE has been demonstrated in a large-scale, Phase III, double-blind, randomised, placebo-controlled clinical trial, RFHE3001, as well as an open-label, single-arm 24-month study RFHE3002 (which recruited both new subjects and subjects who had participated in RFHE3001). The inclusion and exclusion criteria of these trials were designed to mirror the actual patient population in clinical practice as closely as possible: adults with a history of acute episodes of HE due to cirrhosis. The dosage regimen investigated in the trials (oral rifaximin at 550 mg BID) corresponds to the licensed dose. The efficacy results of the clinical trials RFHE3001 and RFHE3002 are therefore directly relevant in appraising the clinical effectiveness of rifaximin in its licensed indication.

The primary efficacy outcome of time to first breakthrough overt HE episode clearly shows that patients on rifaximin are less likely to experience a new HE episode, i.e. they are in remission for longer. A reduced rate of HE episodes and longer remissions

represent an evident benefit to patient. There is evidence to suggest that patients who experience HE face a higher mortality risk than patients without HE, the mortality risk increases further with more severe grade of HE (12, 14, 18-20). It is plausible that reducing the recurrence of HE, as is associated with rifaximin treatment, could result in improved overall survival.

The Conn score is the recommended and widely used gold standard for grading the severity of impaired mental status in overt HE (18, 71, 72). The Conn score includes 4 grades and judges symptoms like lethargy, confusion, disorientation and, at worst, coma. A worsening in Conn score is therefore correlated with patient wellbeing. Fatigue, also no doubt an issue for patients, was measured using the CLDQ, which is a widely used QoL instrument in liver disease (73-75).

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

In the clinical trials rifaximin was used at a dose of 550 mg BID, which reflects the licensed dose and dosing frequency for the licensed indication of rifaximin. The entirety of the presented evidence base is therefore for the dose given in the SPC (26). The patient population in the trials was chosen to resemble the patient population in clinical practice, including adults with prior acute episodes of HE due to cirrhosis. The patient population enrolled in the clinical trials may be considered a fair approximation of the UK patient population, having been recruited from the United States, Canada and Russia[6].

The study results presented may not be applicable to patients who are intolerant to lactulose. Furthermore, patients with severe disease, i.e. MELD scores ≥25, have not been included in the presented studies. Although there are indications that rifaximin is also likely to be efficacious in this patient population (70), there are no RCTs that demonstrate this effect.

[6] The trials were conducted in the US, Canada, and Russia, and the population studied was considered acceptable to the EU regulatory authorities as sufficiently reflecting a European setting

7 Cost-effectiveness

Cost effectiveness analysis

- A cost-utility model was developed using a state transition Markov approach to compare the cost effectiveness of rifaximin plus optional concomitant lactulose versus placebo plus optional concomitant lactulose as per the pivotal RCT, RFHE3001 (base case analysis: ITT population study RFHE3001 [rifaximin n=140, placebo n=159]). In study RFHE3001, 91.4% and 91.2% of patients used optional concomitant lactulose in the rifaximin and placebo groups, respectively.
- Subgroup analyses were also undertaken where patients in both the rifaximin and placebo arms have 100% concomitant lactulose use (subgroup A, 91.3% of the ITT population [rifaximin n=128, placebo n=145]) and 0% have concomitant lactulose use (subgroup B, 8.7% of the ITT population [rifaximin n=12, placebo n=14]).
- The model structure was chosen in order to capture outcomes that would be expected in clinical practice and to reflect pivotal trial primary outcome, time to first breakthrough HE episode, and subsequent breakthrough HE episodes following periods of remission.
- The patient population under consideration in the economic evaluation is adults in remission from recurrent episodes of overt HE reflecting the patient characteristics of those observed in the pivotal Phase III RCT for rifaximin and the licensed indication for rifaximin.
- The base case analysis determines the cost effectiveness of rifaximin plus lactulose versus placebo plus lactulose using data from the ITT population in the rifaximin pivotal study RFHE3001.
- The base case analysis demonstrates that rifaximin plus concomitant lactulose provides an additional 0.1875 QALYs at an additional cost of £4,347.50 resulting in an incremental cost effectiveness ratio of £23,186 per QALY gained, compared with placebo plus concomitant lactulose.
- Deterministic sensitivity analysis demonstrated that the model was most sensitive to changes to parameters used in the extrapolation of time to first breakthrough HE episode from the RFHE3001 trial.
- The PSA demonstrated that at a willingness-to-pay threshold value of £30,000 per QALY, the probability of rifaximin being cost effective is 99.6%.

Rifaximin represents a cost-effective treatment option for the reduction in recurrence of episodes of overt HE at a willingness-to-pay threshold of £30,000 per QALY.

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in Section 10.10, appendix 10.

A literature search was conducted in May 2011 to identify relevant economic evaluations that may be relevant to this submission across the following sources: Embase and Medline; the Cochrane Library and the websites of international health technology assessment agencies.

The search strategy is provided in Section 10.10.

The results of the search are presented in Table 20.

Table 20: Results of literature searches of economic literature

	Embase, Medline and Cochrane
Total citations	**47**
Not HE	44
Not an economic evaluation	2
Review	0
Total excluded	46
Include	**1**

Abbreviations: HE, hepatic encephalopathy.

The two citations excluded on the basis of not being economic evaluations were both cost-analyses comparing the outcomes and costs associated with HE hospitalisations in patients treated with rifaximin and lactulose: Leevy and Philips, 2007 (40) and Neff et al, 2006 (76). Both analyses showed that patients receiving lactulose incurred higher hospitalisation costs for the treatment of HE than those treated with rifaximin: US$13,285 for lactulose and US$7,958 for rifaximin in Neff et al, (76); and US$56,635 for lactulose and US$14,222 for rifaximin in Leevy and Philips, 2007 (40).

Search of the CRD retrieved one relevant publication, Huang et al, 2007 (77). This was also retrieved during the search of the Embase, Medline and Cochrane databases. The results of the search are presented in Table 21.

Table 21: Results of literature searches – CRD database

	CRD database
Total citations	**56**
Not HE	23
Not an economic evaluation	6
Review	26

	CRD database
Total excluded	55
Include	**1**

Abbreviations: HE, hepatic encephalopathy.

Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

There was one economic study identified in the literature searches, Huang et al, 2007 (77) a summary is provided in Table 22. The population in Huang et al, does not reflect the current decision problem as per the licensed indication for rifaximin in the UK i.e. reduction in recurrence of episodes of overt HE. Therefore, a de-novo analysis was undertaken.

Table 22: Summary of Huang et al, 2007 (77)

	Huang et al. (2007)
Country and Perspective	USA. Third party payer.
Treatment Pathway	Decision analysis to calculate the cost effectiveness of six treatment strategies in HE; 1. no HE treatment, 2. lactulose monotherapy, 3. lactitol monotherapy, 4. neomycin monotherapy, 5. rifaximin monotherapy, 6. rifaximin salvage therapy.
Economic Analysis	
Type of analysis	CEA and BIA
Resource use and costs	Medication costs; non-medication costs such as doctor visits, laboratory tests, and ultrasonography; and cirrhosis related costs such as out-patient care of persistent HE, hospitalisation for advanced HE, HE related MVA, costs associated with variceal haemorrhage, ascites, liver transplant and follow-up after transplant.
Efficacy	Assessed as the incremental cost per QALY gained between the competing treatment strategies.
Source of utilities	Sourced from Chong et al. 2003[a]
Indirect costs/benefits	Not included.
Discounted	3% per annum.
Economic Model	
Time horizon	Lifetime horizon (mean = 10 years).

	Huang et al. (2007)
Model type	Decision analysis using TriagePro with Markov cycles. Health states included sub-clinical HE, overt HE, clinical response, non-HE complication, liver cancer, liver transplantation and death.
Details to allow replication	Sufficient details provided of methods used.
Results Summary	
Efficacy results	1. The "No treatment" strategy was the least effective and "rifaximin salvage therapy" was the most effective. 2. "Lactulose monotherapy" was the least expensive and "rifaximin monotherapy" was the most expensive. 3. Compared with "Lactulose monotherapy", "rifaximin salvage therapy" cost an incremental US$2,315 per QALY gained.

Abbreviations: BIA, budget impact analysis; BID, twice daily; CEA, cost effectiveness analysis; HE, hepatic encephalopathy; QALY, quality adjusted life year; MVA, motor vehicle accident.

Notes: [a]Chong et al. (2006), health state utilities and quality of life in hepatitis C patients, Am J Gastroenterol, 2006; 101: 2076-2089

Sources: (77)

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996), or Philips Z, et al. (2004). For a suggested format based on Drummond and Jefferson (1996), please see Section 10.11, appendix 11.

A formal quality assessment was not undertaken.

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is (are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in Sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The patient population under consideration in the economic evaluation is adults (≥ 18 years of age) in remission from previous episodes of hepatic encephalopathy (HE). Patients at enrolment in the pivotal study were in remission having had at least two prior episodes of HE, associated with hepatic cirrhosis, (equivalent to Conn score ≥ 2).

The patient population reflects the patient characteristics of those observed in the pivotal study RFHE3001 (Bass et al, 2010) (22), (Table 23) and the licensed indication for rifaximin (reduction in recurrence of episodes of overt HE in patients ≥ 18 years of age). The mean age of the patient population from study RFHE3001 was 56.2 years; therefore this is the starting age of patients in the model.

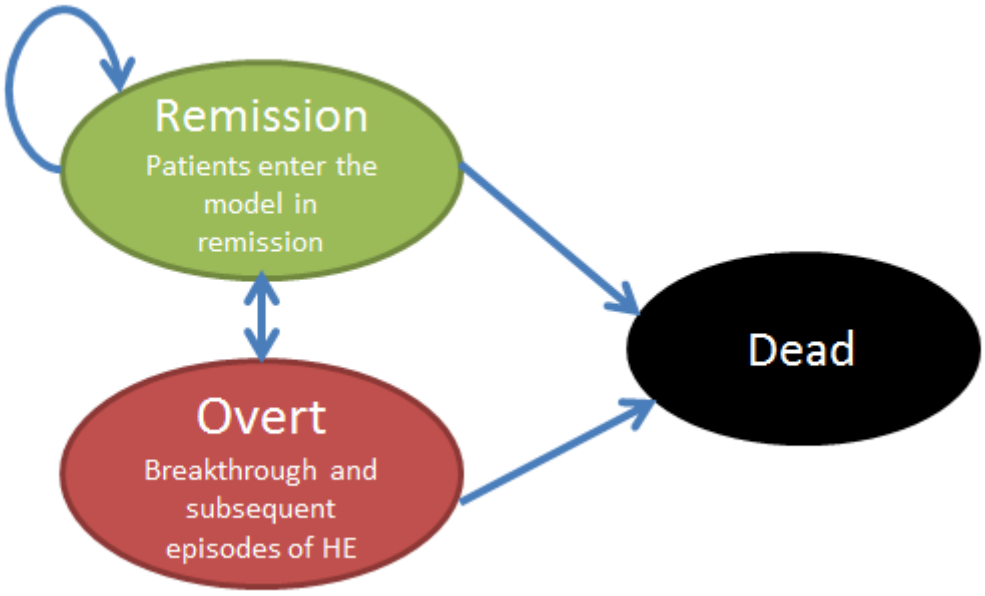
Table 23: Patient characteristics RFHE3001

Characteristic	Rifaximin (N=140)	Placebo (N=159)	Total (N=299)
Mean Age (years)	55.5	56.8	56.2
Male (n)	75	107	182
Female (n)	65	52	117

Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

Figure 13: Model schematic



7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in Section 2.5.

A cost-utility model was developed in Microsoft® Excel 2010 using a state transition Markov approach (as outlined in Section 7.2.2). The structure of the model was considered appropriate and reflected the clinical pathway of the condition according to expert opinion and reflects the pivotal study primary outcome, time to first breakthrough HE episode. In addition subsequent breakthrough HE episodes are captured following periods of remission as observed in UK clinical practice. The base case analysis determines the cost effectiveness of rifaximin plus concomitant lactulose versus placebo

plus concomitant lactulose[7] based on data from the ITT population [rifaximin n=140, placebo n=159] in the rifaximin pivotal study RFHE3001. The pivotal Phase III study (RFHE3001) compares rifaximin with placebo. Patients had the option to use lactulose as concomitant medication during the study, if the patient was receiving lactulose therapy at baseline. In the ITT population 91.4% and 91.2% of patients, took concomitant lactulose in the rifaximin and placebo groups, over 6 months of treatment.

Subgroup analyses were also undertaken on patients in both the rifaximin and placebo arms where all patients received concomitant lactulose (subgroup A, 91.3% of the ITT population [rifaximin n=128, placebo n=145]) and where no patients received concomitant lactulose use (subgroup B, 8.7% of the ITT population [rifaximin n=12, placebo n=14]).

7.2.4 Please define what the health states in the model are meant to capture.

HE is commonly defined based on severity (see Figure 1 in the Executive Summary).

The severity of HE is characterised by clinical symptoms of mental deterioration by Conn grade[8] in which higher scores indicate a higher severity. The ISHEN classification terms patients as either unimpaired, covert (Conn grade 0 or 1) or overt (Conn grade 2, 3 or 4) (16).

To put this into UK context (see Figure 1), expert advisors noted that in UK clinical practice the terms covert and overt are not commonly used. Patients are often referred to as having “minimal HE/remission” (covert) or episodes of “clinically relevant HE” (overt).[9] After an overt episode, patients usually return to an unimpaired or minimal HE state and this is considered to constitute a state of remission.

The health states in the model (remission, overt and dead) were defined in order to capture the disease pathway (also described in detail in Section 2.1) and the clinical endpoints from the pivotal study.

Patients enter the model in remission (patients at enrolment in the pivotal study, were in remission from at least two prior episodes of HE, associated with hepatic cirrhosis, equivalent to Conn score ≥ 2).

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[7] These are termed ‘rifaximin’ and ‘placebo’ throughout this submission

[8] Hepatic encephalopathy can be graded using the Conn grade (also called the West Haven classification) in which higher scores indicate a higher severity, Grade 0-4 where Grade 0 represents: no personality or behavioural abnormality detected – Grade 4: coma (unresponsive to verbal or noxious stimuli). Note Conn grade and Conn score are used interchangeably throughout the document

[9] Throughout the document the terms ‘covert’ ‘minimal HE/remission’ are used interchangeably dependent on the source of the information. Similarly ‘overt’ and ‘clinically relevant HE’ are used interchangeably dependent on the source of the information.

Patients can then transition to the overt state when they experience their first breakthrough episode of HE (as defined in the pivotal study)[10]. Following a breakthrough episode of HE, patients return to the remission state and remain there pending subsequent episodes of HE or death.

Table 24 details the model health states and the definition of each health state.

Table 24: Model health states

Model health state	HE classification
Remission	Remission (Conn score of 0 or 1) In study RFHE3001 (and hence the model) patients were eligible to participate if they had at least two episodes of HE during the previous 6 months and were in remission at study enrolment (Conn score 0 or 1).
Overt	First breakthrough episode of overt HE within the model (an increase from a baseline Conn score of 0 or 1 to a score of 2 or more or from a baseline Conn score of 0 to a Conn score of 1 plus a 1-unit increase in the asterixis grade) AND Subsequent breakthrough episodes of overt HE within the model (an increase from a baseline Conn score of 0 or 1 to a score of 2 or more or from a baseline Conn score of 0 to a Conn score of 1 plus a 1-unit increase in the asterixis grade)
Dead	N/A

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in Section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to Section 2.1.

The model health states capture the main aspects of the disease pathway, that is, recurrent episodes of HE. Whilst rifaximin has a proven effect in reducing the burden and frequency of the symptoms of HE, it has not been proven to change the underlying progression of cirrhosis. Therefore the treatments in the model are not assumed to affect the underlying progression of patients' liver cirrhosis, however, patients' disease will progress over time. This is reflected in the current model by assuming a rate of mortality associated with liver disease (see Section 7.3.2).

[10] Note whilst the primary outcome in the pivotal study is time to first breakthrough episode patients at enrolment were in remission from at least two previous episodes of HE

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 25: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	5 year	The base case analysis presents a five year time horizon in order to adequately capture the health benefits and costs. A shorter time horizon would understate the incremental costs and benefits of rifaximin treatment.	NICE Methods Guide (78)
Cycle length	1 month	In line with the interval at which data were collected during the RFHE3001 clinical trial and was considered sufficiently short to avoid over-estimating outcomes and reflect patients' on-going resource use.	RFHE3001 (27)
Half-cycle correction	No	Half-cycle correction was not applied in the Markov model due to the relatively short cycle length.	N/A
Were health effects measured in QALYs; if not, what was used?	Health effects were measured in QALYs	Recommended in the NICE reference case and the scope for this appraisal	NICE Methods Guide (78)
Discount of 3.5% for utilities and costs	Utilities and costs were discounted at 3.5%	Recommended in the NICE Guide to methods of technology appraisal	NICE Methods Guide (78)
Perspective (NHS/PSS)	UK NHS and PSS	As stated in the decision problem	NICE Methods Guide (78)

Abbreviations: NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years.

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in Sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The comparators listed in the final scope are lactulose, neomycin and neomycin with lactulose.

The base case analysis determines the cost effectiveness of rifaximin plus concomitant lactulose versus placebo plus concomitant lactulose[11] based on data from the ITT population [rifaximin n=140, placebo n=159] in the rifaximin pivotal study RFHE3001. The pivotal Phase III study (RFHE3001) compares rifaximin with placebo. Patients had the option to use lactulose as concomitant medication during the study, if the patient was receiving lactulose therapy at baseline. In the ITT population 91.4% and 91.2% of patients, took concomitant lactulose in the rifaximin and placebo groups, over 6 months of treatment.

The doses for rifaximin and lactulose in the model are as reported per the pivotal study and according to the licensed indication for rifaximin. For lactulose, the recommended dose is 30 to 50mL 3 times daily (79). In the RFHE3001 clinical study, the mean dose of lactulose was 3.14 cups per day for patients on rifaximin and 3.51 cups per day for patients on placebo (1 cup is 10g lactulose/15mL) and rifaximin one 550mg tablet BID.

The economic evaluation does not include neomycin as a comparator treatment in the management of HE for a number of reasons. Neomycin is not licenced for the reduction in recurrence of episodes of overt HE, based on expert opinion it is not routinely used in clinical practice for the prevention of recurrence of HE in remission, but rather for hepatic coma, and there is a lack of clinical trial data and evidence to be found in published literature following a systematic review. The rationale for exclusion is outlined in greater detail in Section 2.7.

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

A clinical continuation rule has not been assumed. The licensed indication for rifaximin is for the reduction in recurrence of episodes of overt HE and therefore patients are anticipated to remain on treatment for the duration of their condition.

7.3 Clinical parameters and variables

7.3.1 Please demonstrate how the clinical data were implemented into the model.

Three health states are included in the model; remission, overt and dead. Transitions between the overt and remission health states were informed by the pivotal and open-label clinical studies (27, 45) as described in Section 6.

[11] These are termed ‘rifaximin’ and ‘placebo’ throughout this submission

Patients enter the model in the remission health state (Conn score of 0 or 1) having previously experienced ≥ 2 episodes of overt HE (equivalent to Conn score ≥ 2). Patients remain in the remission health state until death or they experience their first breakthrough episode of HE (an increase from a baseline Conn score of 0 or 1 to a score of 2 or more or from a baseline Conn score of 0 to a Conn score of 1 plus a 1-unit increase in the asterixis grade). The cycle length in the model for an episode of overt HE is one month, during which a proportion of patients will require hospitalisation based on data from study RFHE3001. At the end of the episode of overt HE and conditional upon the patient not dying, they return to the remission heath state in the model. Patients reside in this health state until death or they experience a subsequent episode. The model allows exponential further episodes of overt HE.

Transitions between the remission and overt health states in the model were derived from survival functions based on time-to-event data from the RFHE3001 clinical study and open-label extension study RFHE3002, as outlined in the clinical-evidence Section 6. The primary efficacy endpoint from study RFHE3001 was time to first breakthrough overt HE episode (classified as the duration from the time of first dose of rifaximin to the first breakthrough overt HE episode). This data governed the transitions from remission to overt health states in the model.

In RFHE3001, the key secondary efficacy endpoint was time to the first hospitalisation involving HE. The percentage of patients hospitalised, having experienced an overt HE episode, was calculated from the study data and applied in the overt states of the model.

Patients can progress to the death state during any cycle and the overt and remission health states in the model. Study RFHE3001 reported that 21 patients died during the study, 11 in the placebo group and 10 in the rifaximin group. However, this was reported over short study duration (six months) and deaths were predominantly reported to be due to conditions associated with disease progression. None of the deaths were considered by the study investigator to be related to the study drug. External sources of data were sourced in order to inform representative disease-related mortality estimates.

There is also evidence to suggest that patients who experience HE face a higher mortality risk than patients without HE, the mortality risk increases further with more severe grade of HE (12, 14, 18-20). It is plausible that reducing the recurrence of HE, as is associated with rifaximin treatment, could result in improved overall survival. Mortality data from RFHE3001 were not sufficiently mature to address the impact of rifaximin on survival.

Whilst the study population reflects patients with HE seen in common clinical settings (District General Hospitals), it doesn’t provide evidence for patients at the more severe end of the disease spectrum. In the economic analysis rather than using the RCT data on mortality, data are taken from other sources Bustamante et al, 1999 and Shawcross et al, 2011 (12, 14) to reflect the whole range of patients who would present with HE in clinical practice.

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Health state transitions

Remission to overt (first breakthrough episode)

The model required transition probabilities for experiencing a first breakthrough episode and subsequent HE episodes over a 5 year time horizon.

The primary efficacy endpoint in study RFHE3001 was the time to first breakthrough overt HE episode as outlined in Section 7.2.4. Subjects discontinued the study at the time of a breakthrough overt HE episode. Patients from RFHE3001 who were treated with rifaximin and maintained remission for the duration of the 6-month study were followed during the open-label study RFHE3002 (45).Time to first breakthrough HE episode for the rifaximin and placebo arms were extracted from a Kaplan-Meier (KM) plot presented in study RFHE3001 for the period 0-168 days (27), see Figure 14. A separate KM plot of time to first breakthrough HE for rifaximin patients who were in remission at the end of the 6-month RCT (RFHE3001) for the period 168 to 1008 days was available from the open label extension study, RFHE3002 (45), (see Figure 15.)

Time to first breakthrough HE data was extracted and combined from both KM plots in RFHE3001 and RFHE3002. Parametric survival distributions were fitted to the combined dataset (RFHE3001 and RFHE3002) for rifaximin patients in order to extrapolate the pivotal study results beyond the final 6 month observation point in the RFHE3001 study (27). Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and visual inspections were also consulted in order to determine best model fit (see Table 26 and Table 27). A Lognormal distribution was used in the base case analysis.

The pivotal study results were extrapolated past the final, 6 month, observation point in the RFHE3001 clinical trial in the placebo arm by fitting a lognormal distribution to the 6 month study data. The shape parameter from this regression was replaced with the shape parameter estimated from the Lognormal distribution fitted to the combined dataset for the rifaximin arm (see Figure 16).Other distributions were tested in sensitivity analyses.

Figure 14: Kaplan-Meier plot time to first breakthrough episode (RFHE3001)

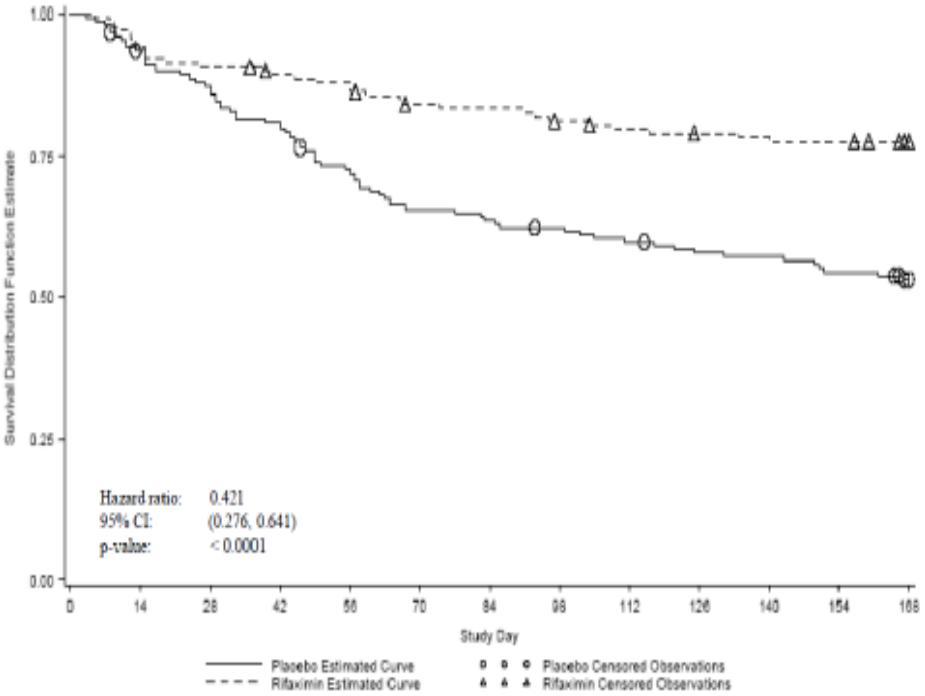


Figure 15: Kaplan Meier Estimates of Distribution of Time to First Breakthrough HE for Continuing Rifaximin Subjects Who Did Not Have an HE Episode in RFHE3001 versus Placebo (n=60)

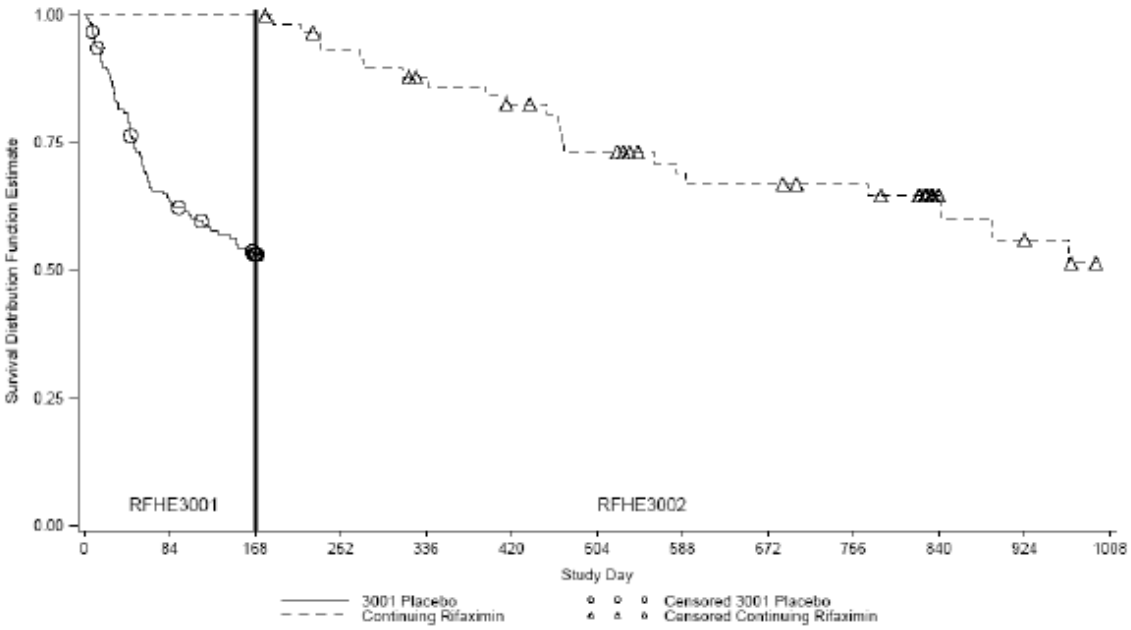


Figure 16: Fitted curves to combined dataset from RFHE3001 and RFHE3002 in order to inform first breakthrough episode (log normal was chosen)

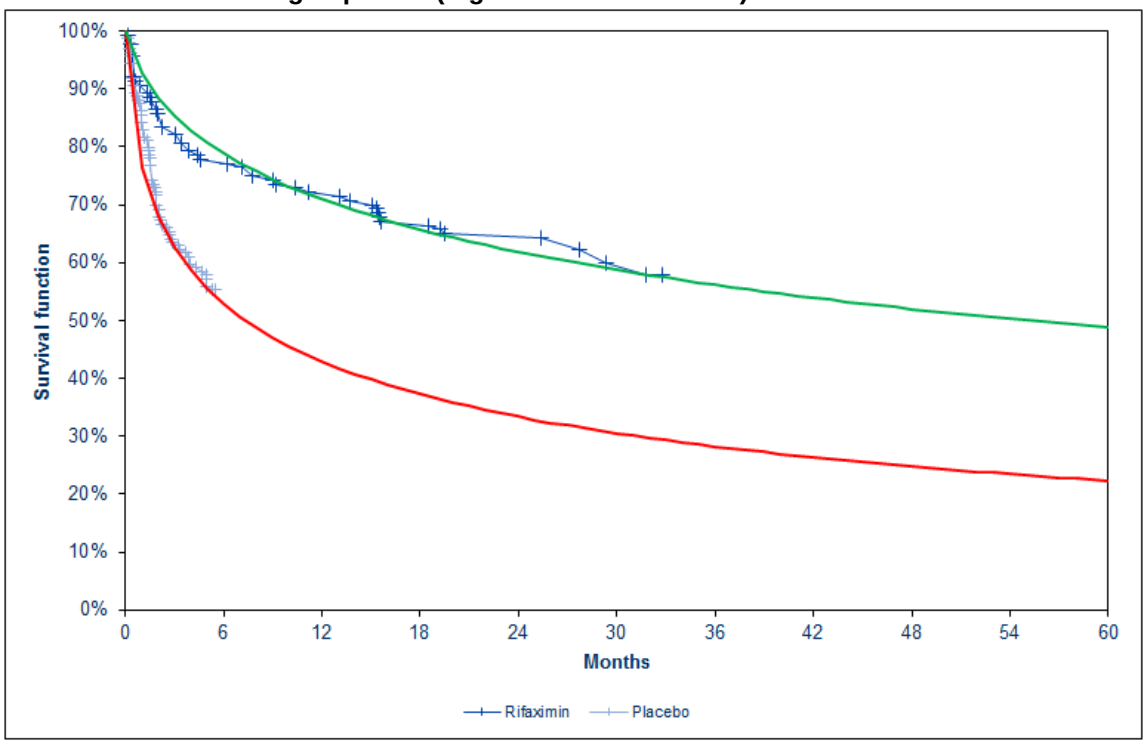


Table 26: Akaike and Bayesian information criterion (fit of the lognormal distribution to the combined dataset for the rifaximin patients

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
exponential	140	-210.9233	-210.9233	1	423.8466	426.7882
weibull	140	-196.0995	-196.0995	2	396.199	402.0823
lognormal	140	.	-193.6976	2	391.3952	397.2785
loglogistic	140	.	-195.4132	2	394.8265	400.7097
gompertz	140	.	-200.2804	2	404.5609	410.4442

Table 27: Regression results for lognormal distribution fitted to the combined dataset for rifaximin patients

_t	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
_cons	4.011754	.3182616	12.61	0.000	3.387972	4.635535
/ln_sig	1.015887	.1045115	9.72	0.000	.8110478	1.220725
sigma	2.761811	.2886411			2.250265	3.389646

Discrete time-dependent transition probabilities were estimated from the instantaneous hazard rates using the formula detailed in Briggs 2006 (80).

Remission to subsequent breakthrough episodes

Time to subsequent episodes, post baseline, is not available from RFHE3001 (27). Therefore, three assumptions have been made:

1. The risk associated with experiencing a subsequent overt HE episode is independent of the risk of preceding episode(s)
2. The risk of subsequent overt HE episodes is independent of time spent in the remission health state
3. The risk of subsequent overt HE episodes is assumed to be constant over time and the same risk reduction for the first breakthrough episode is applied to subsequent episodes.

As per the licensed indication, rifaximin will be used for the reduction in recurrence of overt HE episodes. Clinical experts concurred that in clinical practice patients would continue on rifaximin treatment and it is plausible to assume the same risk reduction for the first breakthrough episode would apply to subsequent episodes.

The data for time to first breakthrough episode were used to inform the risk of experiencing subsequent episodes. An exponential curve was fitted to the digitised data from the Kaplan-Meier plot of time to first breakthrough episode from RFHE3001 study. A HR for rifaximin versus placebo was estimated and applied to the baseline survivor function (placebo) to estimate the survivor function for rifaximin. Time-independent discrete transition probabilities were estimated from the instantaneous hazard rates.

Table 28: Exponential regression

_t	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
RIF	-.8947782	.2152732	-4.16	0.000	-1.316706	-.4728504
_cons	-2.159487	.1186782	-18.20	0.000	-2.392092	-1.926882

Overt to remission

It was assumed that a patient would transition back to the remission state at the end of a cycle after experiencing an overt HE episode if they did not die.

Death

There is evidence to suggest that patients who experience HE face a higher mortality risk than patients without HE, the mortality risk increases further with more severe grade of HE (12, 14, 18-20). It is plausible that reducing the recurrence of HE, as is associated with rifaximin treatment, could result in improved overall survival. Mortality data from RFHE3001 were not sufficiently mature to address the impact of rifaximin on survival.

Whilst, the study population reflects patients with HE seen in common clinical settings (District General Hospitals), it doesn't provide evidence for patients at the more severe end of the disease spectrum. In the economic analysis rather than using the RCT data on mortality, data are taken from other sources Bustamante et al, 1999 and Shawcross

et al, 2011 (12, 14) to reflect the whole range of patients who would present with HE in clinical practice.

The baseline mortality in the model is the additive combination of the HE specific and all-cause mortality as detailed below.

All-cause mortality

The mean age of the patient population under consideration in study RFHE3001 was 56.2 years of age, and adopted in the base case analysis. Patients in the model were assumed to have a baseline risk of all-cause mortality given their mean age and underlying health status. General population age-related mortality rates were applied using the recognised method of extraction from Interim Life Tables for England and Wales by the Office of National Statistics (81) and converted into monthly probabilities. The risk was adjusted to incorporate the weighted average of the ratio of males to females in the RFHE3001 study (60.9% and 39.1% of the ITT population were male and female, respectively).

HE specific mortality

It has been assumed that there is an increased risk of mortality associated with patients' underlying liver disease. Bustamante et al, 1999 (12) reviewed the charts of 111 cirrhotic patients who developed a first episode of acute HE to determine their survival probability and to identify prognostic factors. A KM plot showed cumulative survival up to 48 months. This data was digitised and parametric survival distributions were fitted to extrapolate the mortality risk out to five years. Model fit was based on the AIC, BIC and visual inspection. A Lognormal distribution was chosen for the model and time dependent transition probabilities were estimated using the formula detailed in Briggs 2006 (80).

Mortality is assumed to differ for the overt HE state versus the remission state. The increased risk of death was applied for the full 28-day cycle.

Mortality differs according to the patients' Conn score. The proportion of patients experiencing first breakthrough overt HE episodes with Conn scores of 1, 2, 3 and 4 were calculated from study RFHE3001 across both treatment arms (27).

The mortality risk at each level of Conn score was taken from clinician expert opinion and a publication by Shawcross et al (14). Shawcross et al presented KM estimates of the survival of patients having an episode of overt HE with Conn score 3 and 4. The mortality rate was estimated from the KM plot in Shawcross et al for Conn score 3 and 4 (30 days, the nearest time point to the cycle length in the model). The mortality rates used for each Conn score in the overt state are reported in Table 29.

Table 29: Mortality rates by Conn score in the overt health state

Conn Score	Estimate	Reference
1	5%	Clinician estimate stated negligible, however 5% was assumed in the base case analysis. Mortality in the overt state was required to be equal to or higher than risk of death in the remission state so it couldn't be zero
2	20%	Clinician estimate
3	53.86%	Shawcross et al (14)
4	71.89%	Shawcross et al (14)

Overt HE-related hospitalisation

The key secondary efficacy endpoint in study RFHE3001 was time to first HE-related hospitalisation. HE-related hospitalisation indicates hospitalisations involving an episode of HE. Hospitalisations were reported for 19 of 140 and 36 of 159 subjects (ITT population) for rifaximin and placebo respectively. The relative effect (Hazard Ratio) for rifaximin versus placebo was reported to be 0.5 (p=0.0129).

The clinical trial reports the number of patients experiencing a breakthrough episode as 31 in the rifaximin arm and 73 in the placebo arm. Therefore the percentage of patients hospitalised given they *experience an overt HE episode* is calculated as 19 of 31 and 36 of 73 subjects for rifaximin and placebo respectively. The percentage of HE related hospitalisations given that an overt HE episode occurred at six months was higher in the rifaximin than the placebo arms (61.29% and 49.32% for rifaximin and placebo respectively). The cumulative probability at six months were converted into monthly probabilities (assuming a constant hazard over time). These probabilities were applied to those patients predicted to reach the overt health state (i.e. those that experienced an episode of overt HE).

Table 30: Percentage of patients having a hospitalisation

Treatment	6-month	1-month
Rifaximin	61.29%	14.63%
Placebo	49.32%	10.71%

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Transitions between the remission and overt health states were governed by probabilities of breakthrough episodes of overt HE derived from KM plots reported in study RFHE3001 and therefore were time dependent. Data on potential subsequent events are lacking and therefore a constant probability for on-going overt HE episodes has been assumed. As such, variation in the transition probabilities over the time horizon of the model has been captured as far as possible. See Section 7.3.2.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No intermediate outcomes were used.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the details. Please provide the following details[12]:

Expert opinion was sought from 9 UK hepatologists on inputs used in the model and to estimate values, where necessary. Expert opinion informed a range of model inputs where they were not available from study RFHE3001 and RFHE3002 or in the literature examined. See Section 7.3.8.

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

A list of all variables used in the economic analysis is provided in Table 31.

Table 31: List of variables in the model

Variable	Value	Lower CI	Upper CI	Distribution	Reference to section in submission
Average daily dose of lactulose - placebo arm	52.65	52.25	53.05	Normal	7.2.7
Average daily dose of lactulose - rifaximin arm	47.10	46.75	47.45	Normal	7.2.7
Rifaximin tablet price	£4.63	4.63	4.63	None	7.5.5
Lactulose price (500 mL)	£2.28	2.28	2.28	None	7.5.5
Cost of outpatient visit	£110.68	£110.51	£110.84	Gamma	7.5.6
Frequency of outpatient visits	3.00	1.00	6.00	Normal	7.5.6
Liver Failure Disorders with Interventions	£3,483.86	£3,235.97	£3,731.75	Gamma	7.5.6
Liver Failure Disorders without Interventions	£2,028.42	£1,922.02	£2,134.83	Gamma	7.5.6
Non-Malignant Liver Disorders with Catastrophic CCs	£3,988.26	£3,700.39	£4,276.14	Gamma	7.5.6
Non-Malignant Liver Disorders with Severe CCs	£3,084.07	£2,882.30	£3,285.83	Gamma	7.5.6
Non-Malignant Liver Disorders with Major CCs	£2,421.08	£2,320.36	£2,521.80	Gamma	7.5.6
Non-Malignant Liver Disorders without Major CCs	£1,795.26	£1,715.41	£1,875.12	Gamma	7.5.6
Percentage hospitalised - placebo + lactulose (ITT)	49.32%	37.40%	61.28%	Beta	7.3.2
Percentage hospitalised - rifaximin + lactulose (ITT)	61.29%	42.19%	78.15%	Beta	7.3.2
Percentage hospitalised - placebo (100% concomitant lactulose, 91.3% of the ITT)	50.00%	37.80%	62.20%	Beta	7.9.3

[12] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Variable	Value	Lower CI	Upper CI	Distribution	Reference to section in submission
Percentage hospitalised - rifaximin (100% concomitant lactulose, 91.3% of the ITT)	62.07%	42.26%	79.31%	Beta	7.9.3
Percentage hospitalised - placebo (0% concomitant lactulose, 8.7% of the ITT)	33.33%	0.84%	90.57%	Beta	7.9.3
Percentage hospitalised - rifaximin (0% concomitant lactulose, 8.7% of the ITT)	100.00%	100.00%	100.00%	Beta	7.9.3
Length of stay (placebo)	5.00	2.00	11.00	Normal	2.5
Length of stay (rifaximin)	5.00	2.00	11.00	Normal	2.5
EQ-5D population norm (all population)	0.86	0.85226	0.86774	Normal	7.4.9
EQ-5D population norm (population aged <25)	0.94	0.92651	0.95349	Normal	7.4.9
EQ-5D population norm (population aged 25-34)	0.93	0.91929	0.94071	Normal	7.4.9
EQ-5D population norm (population aged 35-44)	0.91	0.89676	0.92324	Normal	7.4.9
EQ-5D population norm (population aged 45-54)	0.85	0.81440	0.88560	Normal	7.4.9
EQ-5D population norm (population aged 55-64)	0.80	0.77684	0.82316	Normal	7.4.9
EQ-5D population norm (population aged 65-74)	0.78	0.75693	0.80307	Normal	7.4.9
EQ-5D population norm (population aged 75+)	0.73	0.70014	0.75986	Normal	7.4.9
Wong 1998 - remission utility	0.82	0.61500	1.00000	Beta	7.4.9
Duration of episode (utility) - lactulose	11	1	28	Normal	7.4.9
Duration of episode (utility) - rifaximin	11	1	28	Normal	7.4.9
Lognormal regression treatment parameter (ITT) (first breakthrough episode)	1.0997970	0.51689	1.68270	MVN	7.3.2
Lognormal regression constant parameter (ITT) (first breakthrough episode)	2.07	1.67	2.47	MVN	7.3.2
Lognormal regression /ln_sig paramter (ITT) (first breakthrough episode)	0.70	0.54	0.86	MVN	7.3.2
Lognormal regression sigma parameter (ITT) (first breakthrough episode)	2.01	1.71	2.36	None	7.3.2
Lognormal regression treatment parameter (ITT) (subsequent breakthrough episode)	-0.91	-1.34	-0.49	MVN	7.3.2
Lognormal regression constant parameter (ITT) (subsequent breakthrough episode)	-2.22	-2.45	-1.98	MVN	7.3.2
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal regression constant parameter (mortality)	1.98	1.60	2.35	MVN	7.3.2
Lognormal regression /ln_sig paramter (mortality)	0.67	0.51	0.82	MVN	7.3.2
Lognormal regression sigma parameter (mortality)	1.95	1.65	2.26	MVN	7.3.2
Percentage of patients with Conn score 0 at baseline	0.68	0.63	0.74	Beta	7.3.2

MVN: multi-variate normal

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.

The study duration of RFHE3001 was 6 months. The base case time horizon employed in the model was five years and costs and clinical outcomes were extrapolated beyond

the 6 month study data. The mean age of HE patients in RFHE3001 is 56.2 years and based on expert opinion allows for an assumption of effect and benefit of treatment beyond 6 months (up to 5 years). Longer-term outcomes associated with the use of rifaximin are available from the open-label extension study RFHE3002, as outlined in Section 6. The outcomes from the longer-term follow up of patients treated with rifaximin allow justification for examining the longer-term effects of treatment of HE. Data from RFHE3002 aids in informing the extrapolation of costs and clinical outcomes beyond the initial 6 month study period (RFHE3001). The extrapolation assumptions used were validated by expert opinion. The details of the method of extrapolation have been described previously in Section 7.3.2.

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Assumption	Justification
Clinical endpoints	
Extrapolation of treatment effect after 6 months	The open label extension RFHE3002 gives evidence to support the assumption of an extended treatment effect (for rifaximin). Supported by expert opinion Rifaximin is assumed to have an effect on probability of experiencing the first overt episode, not just for 6 months but up to 5 years
Time to subsequent breakthrough HE episodes based on time to first breakthrough HE episode data	Time to first breakthrough HE episode was the primary endpoint in study RFHE3001. Time to subsequent breakthrough HE episodes was not recorded in the pivotal study. The risk of subsequent overt HE episodes is assumed to be constant over time and the same risk reduction for the first breakthrough episode is applied to subsequent episodes. Rifaximin as per the licensed indication is assumed to reduce the recurrence of subsequent episodes of HE. Expert opinion concurred that in clinical practice patients would continue on rifaximin treatment and there is no clinical reason why the same risk reduction for the first breakthrough episode would not apply to subsequent episodes.
HE-related hospitalisation - cumulative rates of being hospitalised at 6 months from the pivotal trial converted into monthly rates	RFHE3001
Assumed increased risk of mortality compared with the general population due to underlying liver disease	Based on expert opinion and Bustamante 1999 (12)
Assumed increased risk of mortality associated	Based on expert opinion and Shawcross et al

Assumption	Justification
with being in the overt HE health state which differs between severities of episodes (by Conn score) and lasting for the full 28 day cycle	(14)
Resource use	
Frequency of covert HE outpatient attendance was assumed to be one visit every 3 months	Based on expert opinion
Mean length of stay for overt HE hospitalisation assumed to be 5 days	Based on expert opinion
Duration of overt HE episode was assumed to last for 11 days	Based on expert opinion
Monthly rates of hospitalisation given overt HE episode has occurred is 14.63% and 10.71% for rifaximin and lactulose, respectively	Proportion of hospitalised patients are assumed to enter hospital due to an episode of overt HE from study RFHE3001 (27)
Costs	
Patients in the model were assumed to receive rifaximin / lactulose and therefore incurred the associated costs for the duration of the model	expert opinion
A weighted average price of unit costs for overt HE is applied based on HRG procedure codes starting GC from NHS Reference Costs 2011/12	Range of codes available for liver disorders
Compliance 100%	Assumption. A sensitivity analysis was conducted to reflect compliance in the pivotal trial (84.3%)
Utilities	
Being in the overt versus remission state is assumed to have an effect on utility, the effect is assumed to last for 11 days. Although an episode is assumed to last for 5 days, expert opinion suggested that patients' QoL would be affected for a few days before and after the episode.	Based on expert opinion
Utilities were age adjusted using data from Kind et al 1999 (82) – UK population norms for EQ-5D	Based on expert opinion. A sensitivity analysis was conducted in which the age adjustment was removed

7.4 Measurement and valuation of health effects

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

HE is a severe and debilitating brain disorder that results from cirrhosis due to varying aetiologies. Recurrent bouts of overt HE negatively impact patients daily functioning and quality of life (10).

Several studies have already demonstrated that chronic liver disease causes profound impairment of patients HRQoL and that these are directly correlated to repeated hospitalisations, severity of disease and complications of cirrhosis such as recurrent overt HE (6-9, 83). Currently there are minimal, long term, controlled studies assessing the impact of HE on HRQoL in cirrhotic patients.

HE is a spectrum of neurological based dysfunctions which affects patient's activities of daily living and decrease the ability to for self-care amongst others. It is these aspects along with the underlying cirrhosis which present the greatest challenge to patients and carers alike.

Cirrhotic patients with previous HE are a significantly higher burden on their caregivers and this is proportional to their cognitive dysfunction (11).

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition

Cirrhosis places a significant financial, socioeconomic, and personal burden on patients and their caregivers (11).

Hepatic encephalopathy (HE) is a significant complication of cirrhosis in terms of effect on patients' functioning. Patients with HE are cognitively impaired and have poor quality of life (11).

Patients in remission from HE have an underlying risk of experiencing breakthrough overt HE episodes. Data from Sanyal et al 2011 indicate that such episodes are associated with impairment of HRQL (10). Therefore, over the course of the condition, a patient's HRQL is likely to decline at any time, depending on the patient's underlying risk of experiencing a breakthrough overt HE episode.

Research also indicates that if not prevented, episodes of HE can reoccur and progress in severity. Increases in the frequency and severity of such episodes predict an increased risk of death (12, 13).

One UK-based study, published in 2011 by Shawcross and colleagues, prospectively evaluated 100 consecutive emergency admission episodes of patients with cirrhosis whose severe HE (Conn score of 3 or 4) was the primary indication for admission to the Liver ICU at King's College Hospital in the London (14). Of these patients, just 52 (52%) survived their first ICU stay while the remainder developed progressive multiorgan failure and died. Overall hospital survival was even lower at 38% (14).

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in Section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

Study RFHE3001 did not include a generic preference based measure of quality of life, or direct elicitation method that could be used to derive utility values for patients with HE receiving treatment with rifaximin HE (with or without lactulose). While data were collected using the SF-36, there are difficulties in getting patients to self-rate their health at the right time i.e. whilst experiencing an overt episode. Moreover, completion of the SF-36 occurred at discrete time points (every 28 days). Therefore given the short duration and infrequent occurrence of episodes of HE, it is unlikely that the use of a generic instrument such as the SF-36 at discrete intervals would have captured the detrimental QoL effects associated with HE episodes.

It was therefore necessary to explore alternative utility values from the published literature.

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

N/A

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

A search was initially conducted of the Embase, Medline and Cochrane libraries in May 2011. This was updated in February 2012 using PubMed with the following search terms: “hepatic encephalopathy” AND “(utility weight) OR (utility value) OR (preference weight) OR (quality of life weight)”, and limited to publications from 1 May 2011 onwards. A total of 74 unique citations were retrieved. Review of those citations focused on identifying publications that presented utility weights in patients with HE. Citations were excluded from further review if they:

- Were not reporting on HE;
- Were QoL studies that did not report preference based utility weights (publications which were based on transformations of HRQoL instruments to utilities were excluded), or did not report utility values; or
- Were not a QoL study.

The search strategy is provided in Section 10.12. The results of the search are presented in Table 32.

Table 32: Results of literature searches - utilities

	Embase and Medline
Total citations	**74**
Not HE	5
Not preference based utility measures	27
Not quality of life study (reviews etc.)	42
Total excluded	74
Include	**0**

Abbreviations: HE, hepatic encephalopathy.

7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

It is very difficult to source utility data as per the NICE reference case, because of the acute nature of the health states, and the low levels of health for the overt state.

No citations were identified which explicitly reported the outcomes of QoL analyses in patients with overt HE. However, two citations were reviewed which referred to cost-utility analyses which included HE as one of the health states (Rubenstein et al, 2004 (84) and Huang et al, 2007 (77)). Huang et al, 2007 used a utility value of 0.60 for the HE health state. This value was drawn from a patient reported standard gamble (SG) exercise among nine patients with decompensated cirrhosis, some of which may have reported at least one prior HE event (Chong et al, 2003 (85)). The corresponding value for patients with compensated cirrhosis was 0.80. For the purposes of the current analysis, the value reported by Chong et al, 2003 may not be appropriate since it does not relate to the disutility of an actual HE event, but rather applies to patients with a history of at least one such event.

Rubenstein et al, 2004 (84) referred to four publications as potential sources of utility values for HE: Bennett et al, 1997 (86), Wong et al, 1998 (87), Younossi et al 2001 (5), Chong et al, 2003 (85). Chong et al, 2003 (85) is as discussed above. Review of the publication by Younossi et al, 2001 revealed that HE was not included as a specific health state or descriptor in the assessment of utilities. It is therefore excluded from further consideration from this analysis. Wong et al, 1998 (87) asked six hepatologists to complete a standard gamble (SG) and time trade off (TTO) task in which one of the health states described was HE. The value reported for that health state is 0.53, with a value of 0.82 for compensated cirrhosis. The authors do not provide any details of the health state descriptors use, nor whether the reported utility values were those derived using the SG or TTO methods. Similarly, Bennett et al, 2007 (86) asked a panel of six hepatologists to complete a TTO exercise to evaluate a number of health states for liver disease – including HE. The resulting utility values were 0.3 for HE and 0.7 for compensated cirrhosis.

To conclude, the only estimates from the literature for the remission and overt states were from panels of hepatologists, no mapping studies were available. Hence there is a justification for eliciting utility values for relevant health states from the public using two appropriate elicitation techniques, time trade off (TTO) approach and standard gamble (SG). Norgine commissioned a utility study (TTO and SG) in order to derive appropriate utility values for use in the economic model (88). TTO utility values were used in the

base case analysis and SG utility values were explored in sensitivity analysis. The details of this study are provided in Section 7.4.9.

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

N/A

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

N/A

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in Sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Utility study – methods (88)

Descriptions of five hepatic encephalopathy-related health states (i.e. Conn score 0, Conn score 1, Conn score 2, Conn score 3 and Conn score 4) were developed in collaboration with Norgine using published literature. Each health state described the typical patient experience across several domains including symptoms, treatment, response, management and prognosis, enabling a balanced description across all five health states. The health states were refined after iterative review by clinicians and piloting the descriptions among a sample of 20 members of the general public in the UK. Each health state description (see below 1) was designed to be easily understood by the general public.

The study was undertaken among a sample of 200 randomly selected members of the general public at different locations across Greater London, UK. Respondents had to be aged between 35 and 65 years of age with or without any liver disease. Potential respondents were excluded if they were not English-speaking, or if they had apparent cognitive impairment, or if in the interviewers' opinion they were incapable of understanding the task (n=1). Additionally, respondents who failed to provide TTO and SG values (n=3) were excluded.

Recruitment occurred during January 2013 and none of the respondents received any remuneration for their participation.

Data were collected through individual, face-to-face interviews, which were conducted using an interview script. At the start of the interview the nature of the questionnaire was explained, after which participants were asked a range of socio-demographic questions about themselves. Participants were then asked to read a short, non-technical description of hepatic encephalopathy and the five different health states. Afterwards, they were asked what proportion of their remaining lifetime they would be willing to sacrifice in return for not living with the symptoms associated with each of the five health

states being evaluated. The TTO approach was open-ended and the interviewers did not use any props.

While the aim of the study was to elicit preference values using the TTO approach, values were also elicited using the SG approach. This involved asking participants to choose between the certainty of living with the symptoms associated with each health state or gambling on a treatment with two possible outcomes: successful treatment or death. The search procedure used in the SG approach was simple titration and the interviewers used diagrams to help respondents visualise the trade-offs involved. No other props were used. Participants were also asked to rate their current health on a horizontal visual analogue scale (range, 0 to 1).

Utility values (ranging from 1.0 for perfect health to 0 for death) were obtained for the five different health states. Differences between groups were tested for statistical significance using a t-test. The preference values associated with the five different health states were stratified by baseline variables including age, gender, marital status, employment status, annual income, preference value for their current health, whether they had any illness or knew someone with liver disease. Multiple regression was performed to assess the relationship between the aforementioned baseline variables and preference values.

NON-TECHNICAL DESCRIPTION OF HEPATIC ENCEPHALOPATHY

- The liver is an organ in the abdomen that processes nutrients and fluids and removes toxins and harmful substances from the blood.
- Liver cirrhosis is the end result of liver damage caused by alcohol abuse or hepatitis or poor diet or obesity or some bile duct diseases.
- Individuals with liver cirrhosis generally present with an enlarged liver and specific blood tests and scans may be required to confirm a liver problem. A liver biopsy may also be required.
- Damage caused by liver cirrhosis is permanent and the liver cannot return to normal. Therefore, the aim of treatment is to prevent further damage and manage any complications.
- Patients with severe liver cirrhosis can develop hepatic encephalopathy. Symptoms include forgetfulness, confusion, personality changes, problems with muscles and movement of limbs and possibly coma. There are five grades of hepatic encephalopathy and the symptoms affect a patient to varying degrees depending on the grade of disease.
- Treatment usually involves medication and changes to diet and lifestyle. If the symptoms cannot be controlled a liver transplant may be required.
- An estimated 58% of patients usually die within one year of experiencing an episode of hepatic encephalopathy and 77% have usually died within three years.

GRADE 0

- Patients can experience tiredness, itching, loss of appetite, nausea, weight loss and bruising of the skin.
- Patients may also find it difficult to pay attention and their reaction times may be slower than normal, so it can take longer to complete usual daily activities.
- Patients might see their doctor and receive general advice and minimal treatment.
- Very few patients who remain in Grade 0 will die.

GRADE 1

- Patients have the same symptoms as those in Grade 0. However, they may also experience a slight lack of awareness, anxiety, feelings of well-being or happiness.
- These patients may also find it harder to pay attention and have difficulty sleeping and

performing usual daily activities.

- Patients are more likely to see their doctor, who would try to establish the cause of the worsening symptoms, and receive general advice and appropriate medical treatment.
- Very few patients who remain in Grade 1 will die.

GRADE 2

- Patients in Grade 2 have the same symptoms as those in Grade 1. In addition they may feel very tired, lack energy and become forgetful.
- These patients will take longer than normal to perform usual daily activities and may become disoriented and detached from family and friends.
- Their speech may be slow or slurred and they may not respond to questions as normal.
- They may be irritable and more child-like in their behaviour.
- Patients may be hospitalised for a few days for tests to try to establish the cause of the worsening symptoms, and receive appropriate supportive care and medical treatment. Afterwards, patients may or may not return to the way they were before.
- An estimated 20% of patients in Grade 2 will die.

GRADE 3

- Patients in Grade 3 have the same symptoms as those in Grade 2. In addition, they may feel very drowsy or sleepy for long periods or confused and feel as if their brain is unable to function as usual.
- They may be unable to perform usual daily activities, such as reading and writing, and may be unable to respond if someone speaks to them.
- Their body may not be responsive and their speech may be slow or slurred.
- Patients will be hospitalised for a few days or a few weeks for tests to try to establish the cause of the worsening symptoms, and receive appropriate supportive care and medical treatment. Afterwards, patients may or may not return to the way they were before.
- An estimated 56% of patients in Grade 3 will die.

GRADE 4

- Patients in Grade 4 will be unconscious in a coma.
- These patients will be hospitalised for a few weeks or maybe even months.
- They will be given tests to try to establish the cause of the worsening symptoms, and receive appropriate supportive care, including oxygen to help them breathe, as well as medical treatment.
- These patients are unable to perform any daily activities while they are in a coma.
- Patients who survive may or may not return to the way they were before.
- An estimated 75% of patients in Grade 4 will die.

[redacted]

Table 33: [redacted]

[redacted]

Table 34: [redacted]

[redacted]

Table 35: [redacted]

[redacted]

[redacted]

[redacted]

Table 36: [redacted]

Table 37: [redacted]

[redacted]

[redacted]

Table 38: [redacted]

Table 39 [redacted]

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide details. Please provide the following details[13]:

Clinical experts at the Advisory Board did not assess the applicability of values available or estimate any values but did advise on the duration of an episode of overt HE.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Please see Section 7.4.9 for full details of patient HRQL experiences in each of the health states.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No health effects were excluded from the model and subsequent analysis.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Patients enter the model in the remission HE health state i.e. in remission from HE (Conn score of 0 or 1) and having experienced recurrent HE (≥ 2 episodes of HE equivalent to Conn score ≥ 2). The mean age of patients entering the model is 56.2 years with the application of a baseline health state utility of 0.83 (87) and age-adjusted for individuals aged 55-64, taken from the UK EQ-5D norms (82). This accounts for the quality of life declining as the patient ages in the model.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQoL is not assumed to be constant over time in the model as it was adjusted for age. See Section 7.4.12. A sensitivity analysis was conducted where age adjustment was removed.

7.4.15 Have the values in Sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

The only amendments made to utility values in the model were age adjustments. See Section 7.4.12.

[13] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

7.5 Resource identification, measurement and valuation

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to Section 2.

HE is a condition predominantly managed in the secondary healthcare setting. Therefore in the base case model 2011/12 NHS Reference Costs (89) were applied. Procedure codes were selected based on the nature of the condition and expert opinion gathered on resource use for managing patients with HE. Details of the Healthcare Resource Group (HRG) procedure codes used and details of how they have been applied in the model are outlined in Section 7.5.6.

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

See Section 7.5.1.

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in Section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

A systematic review was not undertaken to identify resource data. Estimates of resource use were obtained from expert opinion and costs were taken from standard published sources.

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide details. Please provide the following details[14]:

Expert opinion was sought to provide information on the type and quantity of resource use associated with the covert and overt health states. In particular, expert opinion was collected to estimate the frequency of outpatient visits during the covert health state and the mean length of stay in hospital when a patient experiences an episode of overt HE.

[14] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to Sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in Section 7.2.2.

Drug acquisition costs were included for rifaximin and lactulose as previously discussed in Section 7.2.2. The drug acquisition costs used in the model were based on published package costs from the British National Formulary (79) for lactulose and data on file for rifaximin.

Rifaximin

The dosage of rifaximin was one 550mg tablet twice a day. The unit price of a 56 tablet pack of rifaximin was £259.23 per pack. See Table 40.

Lactulose

The recommended dose for lactulose is 30 to 50mL 3 times daily, and subsequently adjusted to produce 2 to 3 soft stools daily. RFHE3001 study-based dose was used in the model. In the study, the mean dose of concomitant lactulose is 3.14 cups per day for patients on rifaximin and 3.51 cups per day for patients on placebo (1 cup is 10g lactulose/15mL). Given that the price of lactulose is £2.28 per 500mL, the cost of concomitant lactulose is calculated as £6.54 per month for patients on rifaximin, and £7.31 per month for patients on placebo. See Table 40.

No administration cost was applied for the two medications as they are administered orally.

Table 40: Drug acquisition costs

Treatment	Avg. daily dose	Unit size	Unit price	Cost per day	Cost per month	Total cost (per month)	Reference
Rifaximin (mg)	1100	550	£4.63	£9.26	£281.80	**£288.34**	BNF (88)
Lactulose concomitantly used with rifaximin (mL)	47.1	500	£2.28	£0.21	£6.64		BNF (79)
Lactulose concomitantly used with placebo (mL)	52.65	500	NA	£0.24	£7.31	**£7.31**	BNF (79)

Table 41: Unit costs associated with the technology in the economic model

Items	Intervention (confidence interval)	Reference to section in submission	Comparator 1 (confidence interval)	Reference to section in submission
Treatment cost	£288.34	Section 7.5.5	£7.31	Section 7.5.5
Total	£288.34	-	£7.31	-

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in Section 7.2.4.

Remission health state

Expert opinion was sought at the Advisory Board in order to determine the frequency of outpatient visits for patients in remission. Opinion suggested that patients are reviewed every 3-6 months in an outpatient setting. In the base case analysis patients are assumed to be followed-up every three months. The unit cost for an outpatient visit was £110.68 and based on NHS Reference Costs for 2011/12 (89), OPATT HRG procedure code 303 for clinical haematology. With frequency of visits assumed to be every 3 months the total cost applied in the model for the remission health state was £36.89 (Table 42).

Table 42: Remission health state - cost per patient

Resource use	Value	Reference
Secondary care costs		
Cost of outpatient attendance	£110.68	NHS Reference Costs (89)
Frequency of outpatient attendance (visit/month)	1/3 months	Expert opinion
Total cost for remission state	**£36.89**	

Overt health state

The model assumes that all patients with overt HE incur the cost of an outpatient visit based on expert opinion. This cost is £110.68 as in Table 42.

In addition, those patients who had a hospitalisation will incur extra costs. The proportion of patients hospitalised due to an overt HE episode in the model was 14.63% and 10.71% for rifaximin and placebo respectively and the mean length of an inpatient stay was assumed to be 5 days, based on expert opinion from the Advisory Board. To estimate the cost per day in the overt health state, a weighted average of all non-elective inpatient (long stay) HRG procedure codes beginning with GC from NHS Reference Costs 2011/12 was used.

The total cost for a patient in the overt health state is £359.73 and £292.96 for rifaximin and placebo respectively (see tables below for further details).

Table 43: Cost per outpatient attendance for all overt HE patients

Resource use	Value	Reference
Cost of outpatient attendance	£110.68	NHS Reference Costs (89)

Table 44: Total cost per overt episode for patients experiencing hospitalisation

Resource use	Value	Reference
Rate of hospitalisation given overt HE episode has occurred		

Rifaximin	14.63%	RFHE3001 (27)
Placebo	10.71%	RFHE3001 (27)
Mean length of inpatient hospital stay (days)	5	Expert opinion
Weighted cost per non-elective inpatient (long stay)	£340.46	NHS Reference Costs (89)
Cost per overt health state: rifaximin	£249.05	Calculation
Cost per overt health state: placebo	£182.28	Calculation

Table 45: Total cost per overt health state with rifaximin and placebo per patient

Treatment	Total cost
Rifaximin	**£359.73**
Placebo	**£292.96**

Table 46: List of health states and associated costs in the economic model

Health states	Items	Value		Reference to section in submission
		Rifaximin	**Placebo**	
Remission	Technology	£288.34	£7.31	Section 7.5.5
	Outpatient attendance	£36.89	£36.89	Section 7.5.6
Overt	Technology	£288.34	£7.31	Section 7.5.5
	Inpatient hospital stay	£249.05	£182.28	Section 7.5.6
	Outpatient attendance	£110.68	£110.68	Section 7.5.6

Abbreviations: CHE, covert hepatic encephalopathy; OHE, overt hepatic encephalopathy

7.5.7 Please summarise the costs for each adverse event listed in Section 6.9 (Adverse events). These should include the costs of therapies identified in Section 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in Section 7.2.2.

Adverse events (AEs) were not included in the economic analysis. Study RFHE3001 showed no statistically significant differences ($p>0.05$ for all comparisons) between the rifaximin and placebo trial groups. Previous modelling in this area was examined and either AEs were similarly excluded or there was limited evidence available for disutilities associated with AEs. The rationale for exclusion was validated during the Advisory Board with expert opinion leaders who agreed with the approach.

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

None.

7.6 Sensitivity analysis

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

Structural uncertainty within the model has been investigated by allowing the individual parameters in the model to be varied in sensitivity analysis. For example, the parameters that informed the curves fitted to the data in order to inform the extrapolation assumptions have been varied and presented in Section 7.7.7.

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in Section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

All variables (as listed in Section 7.3.6) except the percentage of patients with a Conn score of 1, 2, 3 and 4 at first breakthrough episode were subject to deterministic sensitivity analysis.

The percentage of patients in the clinical trial presenting with each Conn score was used in the model to determine the weighted mortality within the overt health state. This was not completed within the deterministic analysis to avoid the issue of having more or less than 100% of patients distributed across the Conn scores at first breakthrough episode. In order to demonstrate the effect on the model of having more patients present with a more or less severe episode, a scenario analysis was undertaken and presented Section in 7.7.9.

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in Section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

PSA was undertaken on all parameters in the model using distributions outlined in Section 7.3.6.

7.7 Results

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see Section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

An analysis of the number of first breakthrough episodes and number of deaths observed in the clinical trial compared with the model was conducted. The results are shown in Table 47. These were taken from the six month time point in the model and from the six month time point in RFHE3001 (27), in order to compare the data at the same time point.

The number of first breakthrough episodes in the model is lower than in the clinical trial due to differences in mortality, which means that more patients will die prior to their first breakthrough episode in the model when compared with the clinical trial. Additional mortality was added to the model to better reflect the underlying disease progression and deaths in patients with HE in the UK as outlined in Section 7.3.2.

More people die in the model when compared with the clinical trial as shown in Table 47. This is due to the effect of assuming additional mortality in the model in order to better reflect mortality observed in clinical practice. Mortality data from RFHE3001 were not sufficiently mature to address the impact of rifaximin on survival. Whilst the study population reflects patients with HE seen in common clinical settings (District General Hospitals), it doesn't provide evidence for patients at the more severe end of the disease spectrum. In the economic analysis, rather than using the RCT data on mortality, data are taken from external sources to reflect the whole range of patients who would present with HE in clinical practice. Therefore the model more accurately reflects mortality as observed in clinical practice.

Table 47: Summary of model results at six months compared with the RFHE3001 clinical trial outcomes at six months

Outcome	Comparator	Clinical trial result (6 months - RFHE3001 (27))	Model result (at 6 months)
Number of first breakthrough episodes of HE in RFHE3001 (27)	Rifaximin	31	21
	Placebo	73	56
Deaths observed at 6 months	Rifaximin	10	68
	Placebo	11	81

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The Markov traces for rifaximin and placebo are shown in Figure 17 and Figure 18. These figures show the proportion of patients in each of the Markov states over the five year time horizon (each cycle is one month).

Figure 17: Markov trace diagram - rifaximin

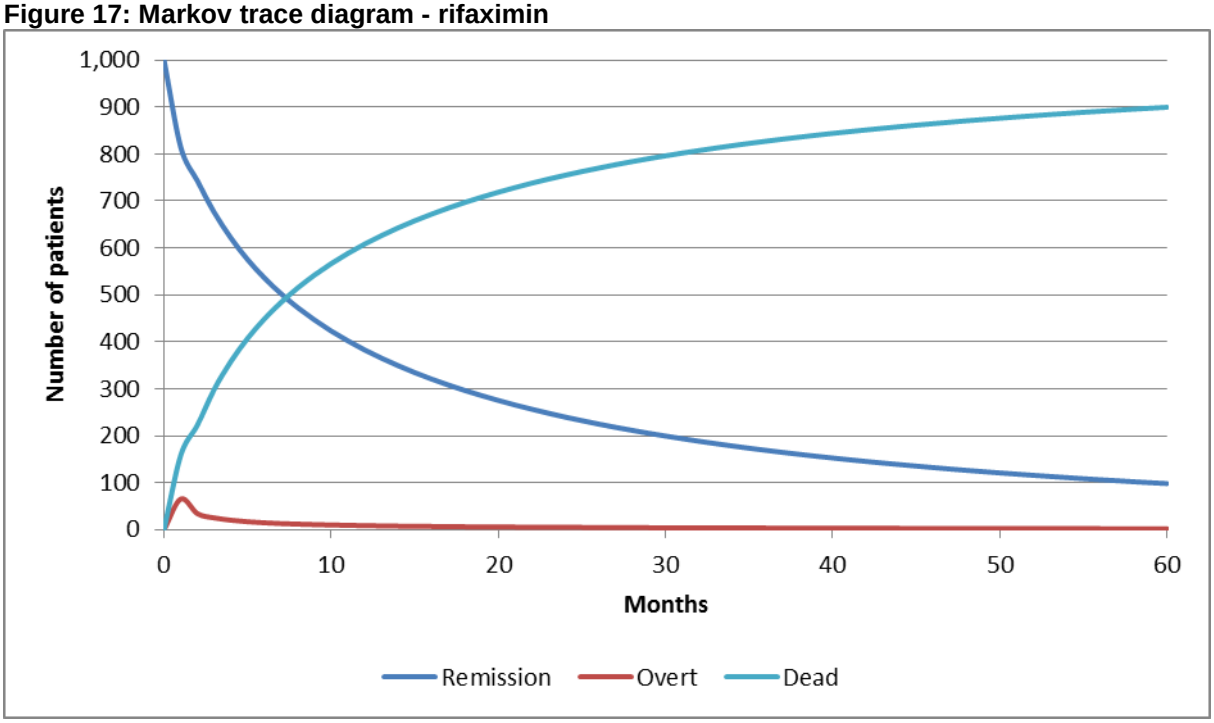
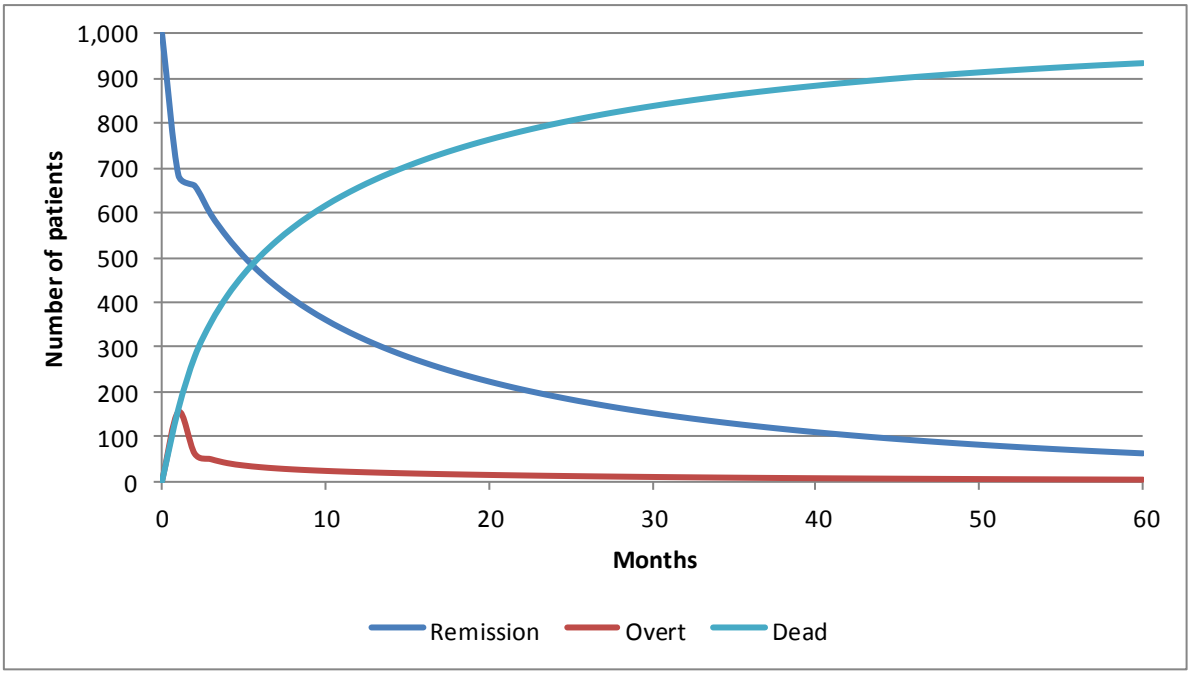


Figure 18: Markov trace diagram – placebo



7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

QALYs are calculated using the utility values for each of the states in the model according to the number of people in each state and the length of time spent in the state.

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

The model is not currently set up to report QALYs for individual outcomes therefore they are not presented here.

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

The model is not currently set up to report disaggregated incremental QALYs and costs by health state or resource use by category of cost therefore they are not presented here.

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Base case results are presented in **Table 48**.

Table 48: Base-case results per patient at 60 months

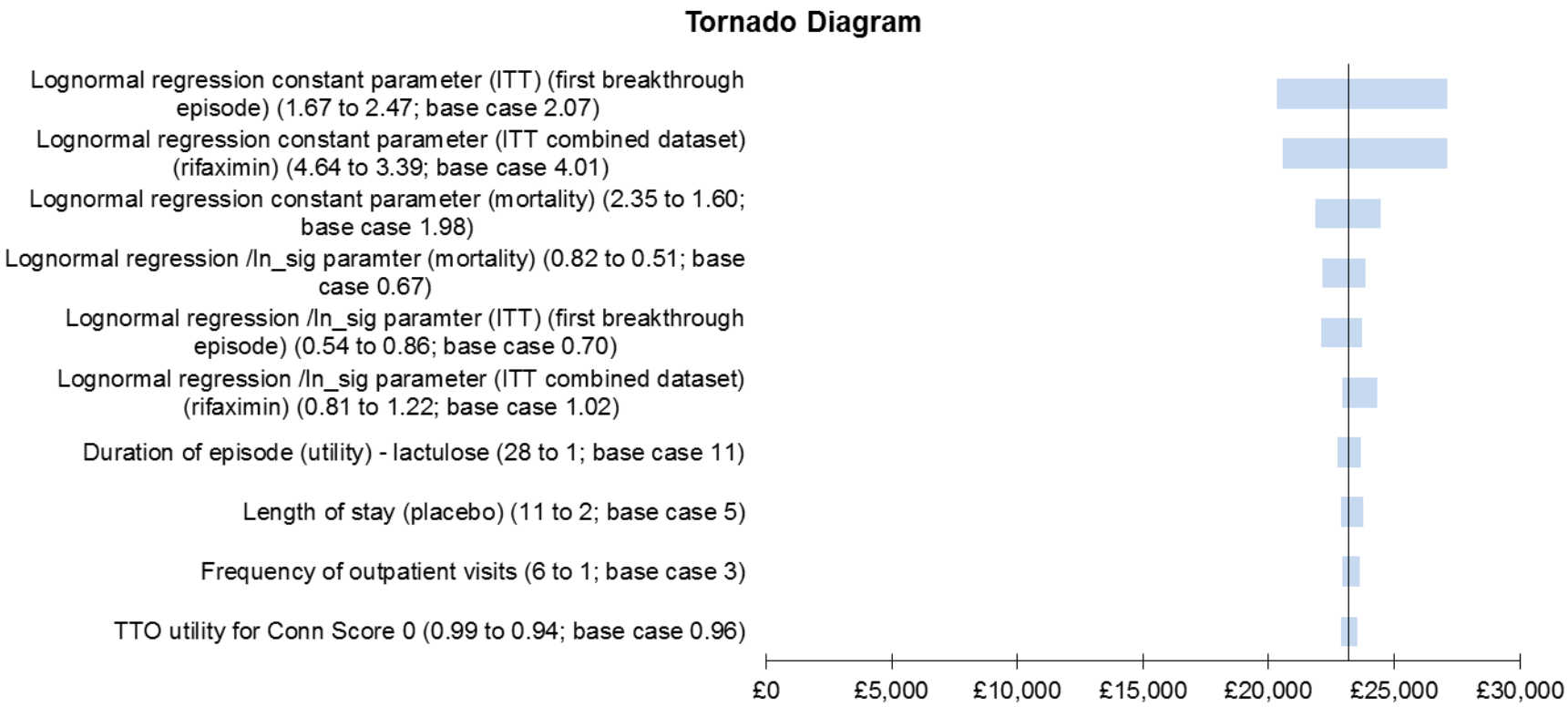
Intervention	Resource use item	Costs	Total QALYS	ICER
Rifaximin	**Drug cost**	**£4,474.27**	**1.2179**	**£23,186**
	Outpatient costs	**£600.24**		
	Inpatient costs	**£93.69**		
	Total	**£5,168.21***		
Placebo	**Drug cost**	**£96.63**	**1.0304**	
	Outpatient cost*	**£555.93**		
	Inpatient cost**	**£168.14**		
	Total	**£820.71***		

Abbreviations: ICER, incremental cost-effectiveness ratio life years gained; QALYs, quality-adjusted life years. *Variances due to rounding in the model.

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Figure 19: Tornado diagram



Abbreviations: ITT, intention to treat; TTO, time trade off lg_sig, log sigma (shape parameter)

A tornado diagram was generated to demonstrate the effect of varying individual parameters on the ICER. The top ten parameters that influenced the ICER when varied in isolation are presented (see Figure 19). The model was most sensitive to changes to shape and scale parameters used in the extrapolation of time to first breakthrough HE episode from the RFHE3001 trial.

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

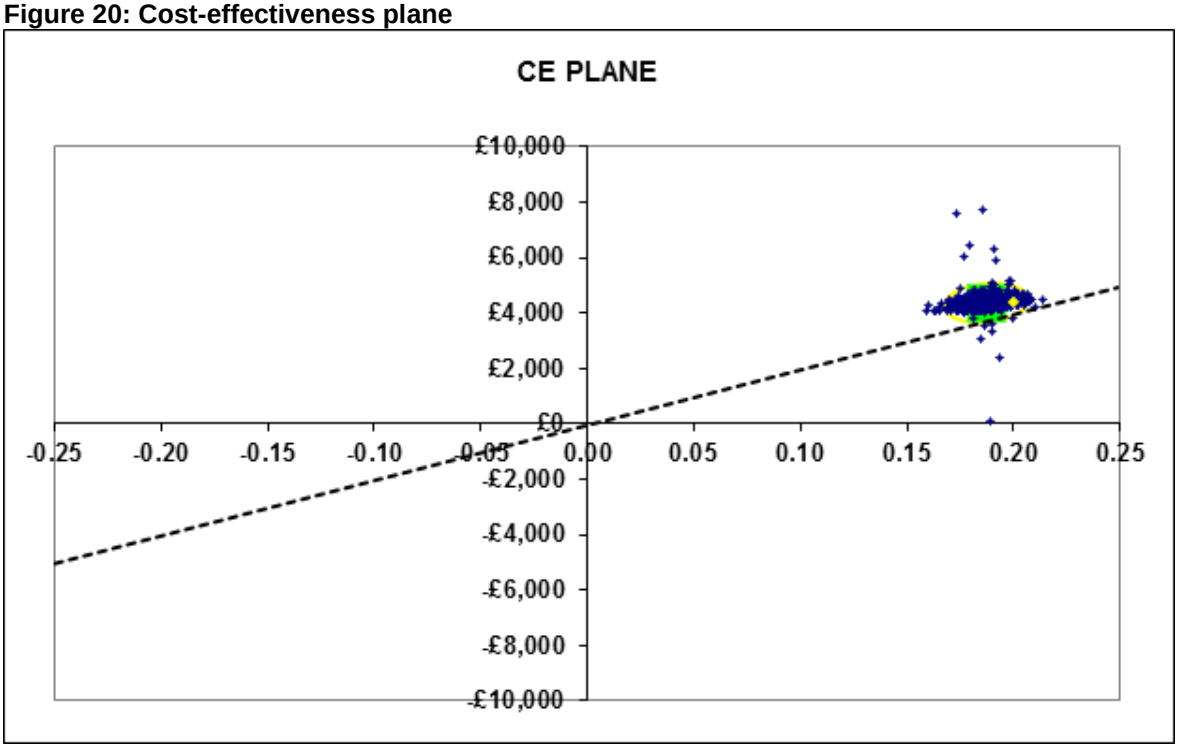
The results of the probabilistic analysis are outlined in Table 49 along with the 95% confidence intervals. The PSA results do not differ substantially from the deterministic results. The ICER for the deterministic analysis was £23,186 and the PSA resulted in an ICER of £23,373.

Table 49: Results of the probabilistic analysis

Intervention	Costs	QALYS	ICER
Rifaximin	£5,337 (CI: £4,818 : £7,099)	1.22 (CI: 1.17 : 1.27)	£23,373 (CI: £21,500 : £26,048)
Placebo	£960 (CI: £539 : £2,397)	1.03 (CI: 0.99 : 1.07)	

Abbreviations: ICER, incremental cost-effectiveness ratio life years gained; QALYs, quality-adjusted life years, CI, confidence interval

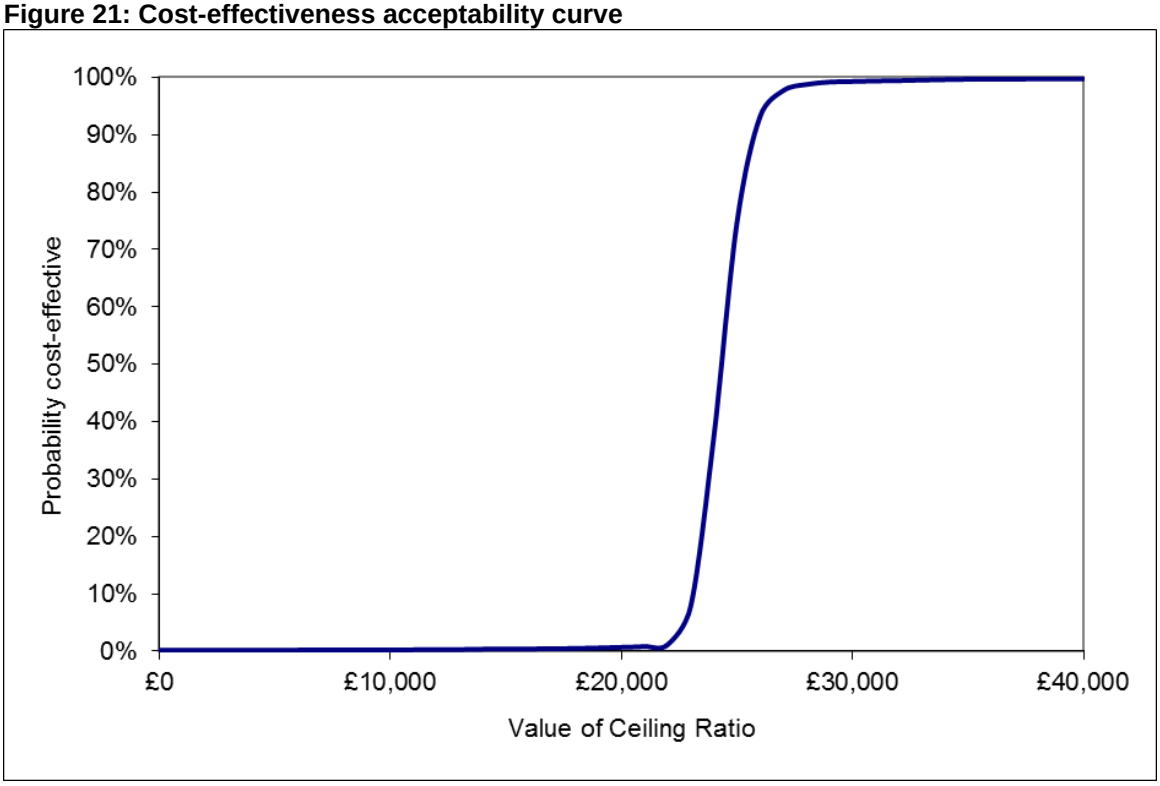
Figure 20: Cost-effectiveness plane



The cost-effectiveness plane is shown in

Figure 20 above. The green square highlights the base case ICER as presented in **Table 48** and the pink square shows the mean incremental cost per QALY from the PSA. One hundred percent of the simulations lie in the North East quadrant indicating that rifaximin used with concomitant lactulose is more costly and more beneficial when compared with placebo.

Figure 21: Cost-effectiveness acceptability curve



At a willingness-to-pay threshold value of £20,000 per QALY the probability of rifaximin being cost effective is 1.60%. At a willingness-to-pay threshold value of £30,000 per QALY the probability of rifaximin being cost effective is 99.60%.

7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Structural sensitivity analysis

Deterministic sensitivity analysis demonstrated that the model is most sensitive to changes in the variables used to inform the fit of curves to the clinical data to estimate time to first breakthrough episode. Consequently, a separate scenario analysis was conducted in order to test the fit of the curve in the model to the clinical data for time to first breakthrough episode.

The analysis was carried out with an exponential curve, Gompertz curve and a Weibull curve. Using the exponential and Gompertz curve, the ICER is reduced to £15,032 and £14,312 per QALY respectively. If the Weibull curve is used, the ICER increases to £28,843 per QALY. The results are outlined in Table 50-Table 52.

Table 50: Results of the model using an exponential curve

Intervention	Costs	QALYS	ICER
Rifaximin	£5,188.92	1.2265	£15,031.73
Placebo	£818.02	0.9357	

Table 51: Results of the model using a Gompertz curve

Intervention	Costs	QALYS	ICER
Rifaximin	£5,167.01	1.2197	£14,310.59
Placebo	£832.13	0.9168	

Table 52: Results of the model using Weibull curve

Intervention	Costs	QALYS	ICER
Rifaximin	£5,175.63	1.2201	£28,843.90
Placebo	£808.03	1.0687	

Scenario analyses

Excluding all-cause mortality

The model takes into account both all-cause mortality and excess mortality as a result of liver disease. This may overestimate mortality in the model if all-cause mortality is already included in the estimates used for disease specific mortality. Therefore a scenario analysis was conducted where the all-cause mortality was excluded from the model. The result of this change on the ICER was minimal as shown in Table 53.

Table 53: Results of the model excluding all-cause mortality

Intervention	Costs	QALYS	ICER
Rifaximin	£5,215.02	1.2290	£23,012.40
Placebo	£826.68	1.0383	

Excluding age-adjustment for utility values

A scenario analysis was conducted in order to test the effect of removing age-adjustment for utility values. The results are shown in Table 54.

Table 54: Results of the model excluding age-adjustment for utility values

Intervention	Costs	QALYS	ICER
Rifaximin	£5,168.21	1.2179	£23,185.87
Placebo	£820.71	1.0304	

Utility values

Data using a generic preference based measure of quality of life measure were not available to populate the economic model. In addition, while data were collected using the SF-36 in the clinical trial, these data were not the most appropriate for use in the model (see Section 7.4.3). Therefore Norgine commissioned a study in order to produce appropriate utility values for the economic model. See section 7.4 for further details of the study conducted (88).

In order to test the effects of utility values on the results of the model, the SG results from the utility study (as opposed to the TTO results) and utility values from the next best

source as identified in the literature, Wong et al, 1998 (87), were used to produce scenario analyses. The results of these scenario analyses are reported in Table 55 and Table 56.

Table 55: Model results using SG utility values from the utility study

Intervention	Costs	QALYS	ICER
Rifaximin	£5,168.21	1.1443	£24,438.56
Placebo	£820.71	0.9664	

Table 56: Model results using published utility values from Wong et al, 1998

Intervention	Costs	QALYS	ICER
Rifaximin	£5,168.21	1.0550	£26,430.75
Placebo	£820.71	0.8905	

Severity of Conn score at first breakthrough episode

The percentage of patients in the clinical trial presenting with each Conn score was used in the model to determine the weighted mortality within the overt health state. In order to demonstrate the effect on the model of having patients present with a more or less severe episode, a scenario analysis was undertaken. In the scenario analysis, it was assumed that severity of episodes was evenly spread across all Conn scores, that is, 25% patients would have a Conn score of 1, 2, 3 and 4). The results are presented in Table 57.

Table 57: Conn score at first breakthrough episode

Intervention	Costs	QALYS	ICER
Rifaximin	£4,899	1.155	**£17,155**
Placebo	£717	0.912	

Compliance

In the base case analysis compliance was 100%. A scenario analysis was conducted in order to incorporate the overall rate of compliance as demonstrated in the clinical trial. Compliance was reported to be 84.3% in the rifaximin arm and 84.9% in the placebo arm in the clinical trial (RFHE3001) (27). The results of this analysis are reported in Table 58.

Table 58: Rifaximin compliance at 84.3%, placebo compliance at 84.9%

Intervention	Costs	QALYS	ICER
Rifaximin	£4,481.05	1.2179	**£19,599**
Placebo	£806.12	1.0304	

Abbreviations: ICER, incremental cost-effectiveness ratio life years gained; QALYs, quality-adjusted life years.

7.7.10 What were the main findings of each of the sensitivity analyses?

The deterministic sensitivity analysis demonstrated that the model was most sensitive to changes to the parameters used in the extrapolation of time to first breakthrough HE episode from the RFHE3001 trial. The PSA demonstrated that, at a willingness-to-pay threshold value of £30,000 per QALY, the probability of rifaximin being cost effective is 99.60%. The scenario analyses conducted showed that the model is robust to changes made to compliance, severity of Conn score, utility values, and the exclusion of all-cause mortality. The model was somewhat more sensitive to changes in the methods used in order to extrapolate the clinical trial data for use in the economic model.

7.7.11 What are the key drivers of the cost-effectiveness results?

The sensitivity analyses demonstrate that the key drivers in model are the parameters used to extrapolate the time to first breakthrough episode from the clinical trial. This is due to the differences between the curves, that is, the magnitude of the treatment effect. Once patients have experienced a first breakthrough episode, they are exposed to the risk of having multiple subsequent episodes and will incur the costs and disutility associated with these episodes. This explains why the fit of the curve to the underlying clinical trial data for time to first breakthrough episode is a key model driver.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The model was validated using a model validation checklist which includes double checking of input parameters, sources and references, and calculations. The model was also validated by an external health economist and reviewer.

7.9 Subgroup analysis

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to Section 6.3.7.

In addition to the economic evaluation comparing rifaximin plus concomitant lactulose versus placebo plus concomitant lactulose as per the full ITT population in the pivotal study (RFHE3001), two subgroup analyses were undertaken where patients in both rifaximin and placebo arms all have concomitant lactulose (subgroup A) and no patients concomitant lactulose use (subgroup B):

- *Subgroup A*: All patients receiving concomitant lactulose in the rifaximin and the placebo groups (i.e. 91.3% of the ITT population in study RFHE3001)

This subgroup was not a pre-planned subgroup analysis in the clinical trial. The analysis is based on direct evidence from study RFHE3001 in which 91.4% of patients in the rifaximin arm (n=128) received concomitant lactulose and 91.2% of patients in the placebo arm (n=145) received concomitant lactulose (27). In order to reflect clinical

practice in which lactulose is expected to be administered with rifaximin (and featured in the wording of Section 4.1 of the SPC) it was considered important to run a subgroup analysis to capture these distinctions.

- *Subgroup B*: Patients receiving no concomitant lactulose in the rifaximin and placebo groups (i.e. 8.7% of the ITT population in study RFHE3001)

This subgroup was not a pre-planned subgroup analysis in the clinical trial. Please note, Subgroup B should be viewed with particular caution as there are only a small number of patients within in each group (rifaximin n= 12 and placebo n=14) and therefore likely to be underpowered, given the smaller number of events involved. This runs the risk of producing spurious differences in treatment effect between the two groups.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

The subgroup analyses presented are not pre-planned and post-hoc analyses were not formally undertaken. Data on time to first breakthrough episode, rate of hospitalisations, proportion of patients with Conn score 0 or 1 at baseline and Conn scores at first breakthrough episode were taken from the RFHE3001 study in order to perform the analyses (see section 7.9.3). Costs in the model remain the same as for the base case analysis with the exception of the removal of the costs associated with lactulose use in subgroup B.

7.9.3 Please describe how the statistical analysis was undertaken.

The following data was used in the subgroup analyses, all other inputs and assumptions were as the base case analysis. Costs in the model remain the same as for the base case analysis with the exception of the removal of the costs associated with lactulose use in subgroup B.

[redacted]

Figure 22: [redacted]

Table 59

Table 60

Table 61:

Table 62

[redacted]

Figure 23 [redacted]

Table 63: [redacted]

Table 64: [redacted]

Table 65: [redacted]

Table 66: [redacted]

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in Section 7.7.6 (Base-case analysis).

Subgroup analyses are presented in Table 67 and Table 68.

Table 67: Subgroup A results – 100% concomitant lactulose use (91.3% of the ITT population)

Intervention	Costs	QALYS	ICER
Rifaximin	£5,044.12	1.1771	**£25,785**
Placebo	£826.25	1.0136	

Abbreviations: ICER, incremental cost-effectiveness ratio life years gained; QALYs, quality-adjusted life years.

Table 68: Subgroup B results – 0% concomitant lactulose use (8.7% of the ITT population)

Intervention	Costs	QALYS	ICER
Rifaximin	£5,356.89	1.2323	**£36,254**
Placebo	£599.79	1.1011	

Abbreviations: ICER, incremental cost-effectiveness ratio life years gained; QALYs, quality-adjusted life years.

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in Section 5.

N/A

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There is a lack of published economic literature that has considered the use of rifaximin for the prevention or treatment of HE. Only one economic evaluation was identified in the systematic review (see Section 7.1.2). No economic evaluations specifically related the prevention of on-going HE episodes were identified (see Section 7.1.2).

Therefore the current economic model provides the only relevant cost utility analysis of rifaximin for the prevention of recurrence of HE in the UK.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in Section 5?

The evaluation covers patients with chronic liver disease who have had prior episodes of overt HE and are currently in remission as per the licensed indication for rifaximin.

In order to reflect clinical practice in which lactulose is expected to be administered with rifaximin (and featured in the wording of Section 4.1 of the SPC) a subgroup analysis containing only those patients who received concomitant lactulose was completed. This analysis demonstrates the cost effectiveness of rifaximin for this group of patients.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Model strengths

The economic evaluation follows the NICE reference case as closely as possible. In defining the decision problem, the scope was followed as outlined and where deviations have occurred, these are justified in the context of available data and clinical opinion.

All comparators for which clinical trials for the population under consideration were available were included. Comparators listed in the scope where included in the search strategies for the systematic literature reviews. Lactulose was included as the comparator in the economic model as this was the only drug for which comparative data (versus rifaximin) could be sourced in the relevant patient population (RFHE3001). Norgine as outlined do not consider that neomycin and neomycin with lactulose are relevant comparators for the reasons previously cited.

Outcomes were extracted from head-to-head RCT data (RFHE3001). RFHE3001 was a well conducted trial with high rates of follow-up. This study differs from previous randomised studies in that it examined the protective effect of rifaximin against breakthrough episodes of HE rather than its effect in the treatment of acute overt episodes of HE (47, 90-93).

The perspective on costs is that of the NHS and PSS and all available costs were used to estimate the health effects on individuals and QALYs were used to estimate health effects on individuals.

In the absence of appropriate HRQL information reported directly by patients (see Section 7.4.3) a TTO exercise was undertaken on 200 members of the general public to estimate utility values for the health states used in the economic model (88).

The discount rate applied was 3.5% for both costs and health effects.

Expert opinion was sought from UK liver specialists to validate the clinical pathway.

Model weaknesses

Many of the weaknesses in the model are due to a lack of available data to inform model inputs. The pivotal study was conducted over a relatively short time period (6 months) and may not capture the full range of patients that may be seen in clinical practice. This meant that the model relied on the input of clinical experts to inform a number of inevitable assumptions required and data sources.

The model does not take into account the potential effect on carer QoL in terms of improved carer well-being and productivity with rifaximin treatment. Therefore the benefits of rifaximin treatment may be underestimated.

There is evidence to suggest that patients who experience HE face a higher mortality risk than patients without HE, the mortality risk increases further with more severe grade of HE (12, 14, 18-20). It is plausible that reducing the recurrence of HE, as is associated with rifaximin treatment, could result in improved overall survival. Mortality data from RFHE3001 were not sufficiently mature to address the impact of rifaximin on survival.

Whilst, the study population reflects patients with HE seen in common clinical settings (District General Hospitals), it doesn't provide evidence for patients at the more severe end of the disease spectrum. In the economic analysis rather than using the RCT data on mortality, data are taken from other sources Bustamante et al, 1999 and Shawcross et al, 2011 (12, 14) to reflect the whole range of patients who would present with HE in clinical practice.

In the absence of data the following further assumptions were also required:

- The risk of experiencing subsequent episodes was assumed constant over time and calculated from primary episode data. This is due to a lack of longer-term comparative data.
- Similarly, the use of an underlying mortality risk which is higher than that seen in the RFHE3001 study, results in a higher number of deaths in the model compared with the clinical trial. This means that more patients die before experiencing an episode.
- Due to a lack of long-term comparative data between rifaximin and placebo, assumptions were made about the shape of the extrapolated RFHE3001 trial data for the placebo arm.
- Then model assumes a continuing treatment effect, but also assumes that those patients that remained alive in the model received ongoing rifaximin / lactulose and therefore incurred the associated costs for the duration of the model

Assumptions used in any economic model could introduce uncertainty in the model results. However, where assumptions were made, expert opinion was sought from UK

liver specialists order to validate the approach taken and to allow the model to reflect clinical reality in the UK as accurately as possible.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Further relevant data for patients who are in remission from HE would enhance the robustness of the model results.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

The number of patients with HE is in England and Wales in uncertain. Chronic liver cirrhosis is caused by several conditions. Statistics are collected separately for each and the occurrence of episodes of HE does not appear to be recorded. A study published in 2008 using information from the General Practice Research Database, reported an estimated prevalence of cirrhosis of 76.3 per 100,000 population aged over 25 years in mid-2001 in the UK (38). Approximately 70% of patients with cirrhosis present with subclinical or mild HE and 23-40% of these may progress to a more severe form of the disease (15-17).

Table 69: Estimation of patients eligible for treatment

	No. of people
Adult population in England and Wales (39)	44,197,700
Prevalence of cirrhosis (76.3/100,000)	33,723
Presenting with subclinical/mild HE	23,606 (70%)
Progressing to more severe form of disease	9,442 (40%)
Eligible for treatment	9,442

For the purposes of estimating the budget impact no rise in incidence is reflected so this may be an underestimation, however also no mortality has been applied which means an overestimation as we know patients die. However, due to the lack of data in this population on yearly incidence and mortality, these have not been applied.

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

No assumptions have been taken about current treatment options the drug cost of rifaximin has only been considered.

8.3 What assumption(s) were made about market share (when relevant)?

N/A.

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

N/A.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Calculations assume a yearly rifaximin cost per patient of £3379.29 (see Table 70).

Table 70: Rifaximin cost per patient per year

Units	Avg. daily dose	Unit size	Units delivered	Unit price	Compliance	Cost per day	Number of days	Yearly cost
mg	1100	550	2	£4.63	100%	£9.26	365	£3,379.29

8.6 Were there any estimates of resource savings? If so, what were they?

No estimate of resource savings were included in the calculations.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

Table 71: Budget impact (drug cost only)

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated % uptake of rifaximin	8%	18%	26%	33%	40%
Eligible for treatment	9,442	9,442	9,442	9,442	9,442
No. treated with rifaximin	755	1,700	2,455	3,116	3,777
Yearly budget impact	£2,552,689	£5,743,309	£8,295,891	£10,529,400	£12,762,909

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Resources savings have not been captured in the budget impact calculations and it is therefore likely that budgetary impact of rifaximin is overestimated. The pivotal study demonstrated that rifaximin reduced the risk of hospitalisation. It is likely that in clinical practice this will translate into a reduction in emergency admissions and length of hospital stay. Two UK centre studies have reported reductions in emergency admissions and hospital length of stay through the use of rifaximin.

[redacted]

Valliani et al, 2012 (25) data on patients prescribed rifaximin for HE between October 2007 and August 2010. Mean length of stay was reported at 14.6 days and 12.4 days and admissions per patient at 2.33 and 1.26 for pre and post rifaximin patients at 12 months, respectively.

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10 Appendices

10.1 Appendix 1

10.1.1 SPC/IFU, scientific discussion or drafts.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

TARGAXAN 550 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 550 mg rifaximin.

Excipients:

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Pink, oval biconvex 10 mm x 19 mm film-coated tablets embossed with “RX” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TARGAXAN is indicated for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age (see section 5.1).

In the pivotal study, 91% of the patients were using concomitant lactulose.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

<u>Posology</u>

Recommended dose: 550 mg twice a day. The clinical benefit was established from a controlled study in which subjects were treated for 6 months. Treatment beyond 6 months should take into consideration the individual balance between benefits and risks, including those associated with the progression of hepatic dysfunction (see sections 4.4, 5.1 and 5.2).

TARGAXAN can be administered with or without food.

Paediatric population

The safety and efficacy of TARGAXAN in paediatric patients (aged less than 18 years) have not been established.

Elderly

No dosage adjustment is necessary as the safety and efficacy data of TARGAXAN showed no differences between the elderly and the younger patients.

Hepatic impairment

No dosage adjustment is necessary for patients with hepatic insufficiency (see section 4.4).

Renal impairment

Although dosing change is not anticipated, caution should be used in patients with impaired renal function (see section 5.2).

Method of administration

Orally with a glass of water.

4.3 Contraindications

Hypersensitivity to rifaximin, rifamycin-derivatives or to any of the excipients listed in section 6.1.

Cases of intestinal obstruction.

4.4 Special warnings and precautions for use

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including rifaximin. The potential association of rifaximin treatment with CDAD and pseudomembranous colitis (PMC) cannot be ruled out.

Due to the lack of data and the potential for severe disruption of gut flora with unknown consequences, concomitant administration of rifaximin with other rifamycins is not recommended.

Patients should be informed that despite the negligible absorption of the drug (less than 1%), like all rifamycin derivatives, rifaximin may cause a reddish discolouration of the urine.

Hepatic Impairment: use with caution in patients with severe (Child-Pugh C) hepatic impairment and in patients with MELD (Model for End-Stage Liver Disease) score > 25 (see section 5.2).

Due to the effects on the gut flora, the effectiveness of oral oestrogenic contraceptives could decrease after rifaximin administration. However, such interactions have not been commonly reported. It is recommended to take additional contraceptive precautions, in particular if the oestrogen content of oral contraceptives is less than 50 μg (see also section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

There is no experience regarding administration of rifaximin to subjects who are taking another rifamycin antibacterial agent to treat a systemic bacterial infection.

In vitro data show that rifaximin did not inhibit the major cytochrome P-450 (CYP) drug metabolizing enzymes (CYPs1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4). In *in vitro* induction studies, rifaximin did not induce CYP1A2 and CYP 2B6 but was a weak inducer of CYP3A4.

In healthy subjects, clinical drug interaction studies demonstrated that rifaximin did not significantly affect the pharmacokinetics of CYP3A4 substrates, however, in hepatic impaired patients it cannot be excluded that rifaximin may decrease the exposure of concomitant CYP3A4 substrates administered (e.g. warfarin, antiepileptics, antiarrhythmics), due to the higher systemic exposure with respect to healthy subjects.

An *in vitro* study suggested that rifaximin is a moderate substrate of P-glycoprotein(P-gp) and metabolized by CYP3A4. It is unknown whether concomitant drugs which inhibit P-gp and/or CYP3A4 can increase the systemic exposure of rifaximin.

The potential for drug-drug interactions to occur at the level of transporter systems has been evaluated *in vitro* and these studies suggest that a clinical interaction between

rifaximin and other compounds that undergo efflux via P-gp and other transport proteins is unlikely (MDR1, MRP2, MRP4, BCRP and BSEP).

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no or limited data from the use of rifaximin in pregnant women.

Animal studies showed transient effects on ossification and skeletal variations in the foetus (see section 5.3).

As a precautionary measure, use of rifaximin during pregnancy is not recommended.

Breastfeeding

It is unknown whether rifaximin/metabolites are excreted in human milk.

A risk to the breast-fed child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from rifaximin therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to male and female fertility.

4.7 Effects on ability to drive and use machines

Dizziness has been reported in clinical controlled trials. However, rifaximin has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Clinical Trials:

The safety of rifaximin in patients in remission from hepatic encephalopathy (HE) was evaluated in two studies, a randomised, double-blind, placebo-controlled phase 3 study RFHE3001 and a long-term, open-label study RFHE3002.

Study RFHE3001 compared 140 patients treated with rifaximin (dose of 550 mg twice daily for 6 months) to 159 patients treated with placebo, while study RFHE3002 treated 322 patients, of whom 152 from the RFHE3001 study, with rifaximin 550 mg twice daily for 12 months (66% of patients) and for 24 months (39% of patients), for a median exposition of 512.5 days.

In addition, in three supportive studies 152 HE patients were treated with varying doses of rifaximin from 600 mg to 2400 mg per day for up to 14 days.

All adverse reactions that occurred in patients treated with rifaximin at an incidence **≥** 5% and at a higher incidence (≥1%) than placebo patients in RFHE3001 are reported in the following table.

Table 1: Adverse reactions occurring in ≥ 5% of patients receiving rifaximin and at a higher incidence than placebo in RFHE3001

MedDRA System Organ Class	**Event**	**Placebo N=159**		**Rifaximin N= 140**	
		n	**%**	**n**	**%**
Blood and lymphatic system disorders	Anaemia	6	3.8	11	7.9
Gastrointestinal disorders	Ascites	15	9.4	16	11.4
	Nausea	21	13.2	20	14.3
	Abdominal pain upper	8	5.0	9	6.4
General disorders and administration site conditions	Oedema peripheral	13	8.2	21	15.0
	Pyrexia	5	3.1	9	6.4
Musculoskeletal and connective tissue disorders	Muscle spasms	11	6.9	13	9.3
	Arthralgia	4	2.5	9	6.4
Nervous system disorders	Dizziness	13	8.2	18	12.9
Psychiatric disorders	Depression	8	5.0	10	7.1
Respiratory, thoracic and mediastinal disorders	Dyspnoea	7	4.4	9	6.4
Skin and subcutaneous tissue disorders	Pruritus	10	6.3	13	9.3
	Rash	6	3.8	7	5.0

Table 2 includes adverse reactions observed in the placebo-controlled study RFHE3001 and long term study RFHE3002, listed by MedDRA system organ class and frequency category.

Frequency categories are defined using the following convention:

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000), Not known (frequency cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse reactions listed by MedDRA system organ class and frequency category.

MedDRA System Organ Class	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations		Clostridial infection, urinary tract infection, candidiasis	Pneumonia, cellulitis, upper respiratory tract infections, rhinitis	
Blood and lymphatic system disorders		Anaemia		Thrombocytopenia
Metabolism and nutrition disorders		Anorexia, hyperkalaemia	Dehydration	
Psychiatric disorders	Depression	Confusional state, anxiety, hypersomnia, insomnia		
Nervous system disorders	Dizziness, headache	Balance disorders amnesia, convulsion, attention disorders hypoesthesia, memory impairment		Anaphylactic reactions, angioedemas, hypersensitivity

MedDRA System Organ Class	Common	Uncommon	Rare	Not known
Vascular disorders		Hot flush	Hypertension, hypotension	Presyncope, syncope
Respiratory, thoracic, and mediastinal disorders	Dyspnoea	Pleural effusion	Chronic obstructive pulmonary disease	
Gastrointestinal disorders	Abdominal pain upper, abdominal distension, diarrhoea, nausea, vomiting, ascites	Abdominal pain, oesophageal varices haemorrhage, dry mouth, stomach discomfort	Constipation	
Hepatobiliary disorders				Liver function tests abnormalities
Skin and subcutaneous tissue disorders	Rashes, pruritus			Dermatitis, eczema
Musculoskeletal and connective tissue disorders	Muscle spasms, arthralgia	Myalgia	Back pain	
Renal and urinary disorders		Dysuria, pollakiuria	Proteinuria,	

General disorders and administration site conditions	Oedema peripheral	Oedema, pyrexia	Asthenia	
Investigations				International normalised ratio abnormalities
Injury, poisoning and procedural complications		Fall	Contusions, procedural pain	

4.9 Overdose

No case of overdose has been reported.

In clinical trials with patients suffering from traveller's diarrhoea doses of up to 1800 mg/day have been tolerated without any severe clinical sign. Even in patients/subjects with normal bacterial flora rifaximin in dosages of up to 2400 mg/day for 7 days did not result in any relevant clinical symptoms related to the high dosage.

In case of accidental overdose, symptomatic treatment and supportive care are suggested.

5 PHARMACOLOGICAL PROPERTIES

TARGAXAN contains rifaximin (4-desoxy-4'methyl pyrido (1',2'-1,2) imidazo (5,4-c) rifamycin SV), in the polymorphic form α.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: intestinal, anti-infective - antibiotics - ATC code: A07AA11.

<u>Mechanism of action</u>

Rifaximin is an antibacterial drug of the rifamycin class that irreversibly binds the beta sub-unit of the bacterial enzyme DNA-dependent RNA polymerase and consequently inhibits bacterial RNA synthesis.

Rifaximin has a broad antimicrobial spectrum against most of the Gram-positive and negative, aerobic and anaerobic bacteria, including ammonia producing species. Rifaximin may inhibit the division of urea-deaminating bacteria, thereby reducing the

production of ammonia and other compounds that are believed to be important to the pathogenesis of hepatic encephalopathy.

Mechanism of resistance

The development of resistance to rifaximin is primarily a reversible chromosomal one-step alteration in the *rpoB* gene encoding the bacterial RNA polymerase.

Clinical studies that investigated changes in the susceptibility of intestinal flora of patients affected by traveller's diarrhoea failed to detect the emergence of drug resistant Gram-positive (e.g. *enterococci*) and Gram-negative (*E. coli*) organisms during a three-day course of treatment with rifaximin.

Development of resistance in the normal intestinal bacterial flora was investigated with repeated, high doses of rifaximin in healthy volunteers and Inflammatory Bowel Disease patients. Strains resistant to rifaximin developed, but were unstable and did not colonise the gastrointestinal tract or replace rifaximin-sensitive strains. When treatment was discontinued resistant strains disappeared rapidly.

Experimental and clinical data suggest that the treatment with rifaximin of patients harbouring strains of *Mycobacterium tuberculosis* or *Neisseria meningitidis* will not select for rifampicin resistance.

Susceptibility

Rifaximin is a non-absorbed antibacterial agent. *In vitro* susceptibility testing cannot be used to reliably establish susceptibility or resistance of bacteria to rifaximin. There are currently insufficient data available to support the setting of a clinical breakpoint for susceptibility testing.

Rifaximin has been evaluated *in vitro* on several pathogens including ammonia producing bacteria as *Escherichia coli* spp, *Clostridium* spp, *Enterobacteriaceae*, *Bacteroides* spp. Due to the very low absorption from the gastro-intestinal tract rifaximin is not clinically effective against invasive pathogens, even though these bacteria are susceptible *in vitro*.

Clinical efficacy

The efficacy and safety of rifaximin 550 mg twice daily in adult patients in remission from HE was evaluated in a phase 3 pivotal, 6-month, randomised, double-blind, placebo-controlled study RFHE3001.

Two-hundred ninety-nine subjects were randomised to treatment with rifaximin 550 mg twice daily (n=140) or placebo (n= 159) for 6 months. More than 90% of the subjects in both groups received concomitant lactulose. No patients were enrolled with a MELD score > 25.

The primary endpoint was the time to first breakthrough overt HE episode and patients were withdrawn after a breakthrough overt HE episode. Thirty-one of 140 subjects (22%) of rifaximin group and 73 of 159 (46%) subjects of placebo group experienced a breakthrough overt HE episode during the 6-month period. Rifaximin reduced the risk of HE breakthrough by 58% ($p< 0.0001$) and the risk of HE-related hospitalizations by 50% ($p< 0.013$), compared with placebo.

The longer-term safety and tolerability of rifaximin 550 mg twice daily administered for at least 24 months was evaluated in 322 subjects in remission from HE in study RFHE3002. One hundred fifty-two subjects rolled over from RFHE3001 (70 from the rifaximin group and 82 from the placebo), and 170 subjects were new. Eighty-eight percent of patients were administered concomitant lactulose.

Treatment with rifaximin for periods up to 24 months (OLE study RFHE3002) did not result in any loss of effect regarding the protection from breakthrough overt HE episodes and the reduction of the burden of hospitalization. Time to first breakthrough overt HE episode analysis showed long-term maintenance of remission in both groups of patients, new and continuing rifaximin.

5.2 Pharmacokinetic properties

Absorption

Pharmacokinetic studies in rats, dogs and humans demonstrated that after oral administration rifaximin in the polymorph α form is poorly absorbed (less than 1%). After repeated administration of therapeutic doses of rifaximin in healthy volunteers and patients with damaged intestinal mucosa (Inflammatory Bowel Disease), plasma levels are negligible (less than 10 ng/mL). In HE patients, administration of rifaximin 550 mg twice a day showed mean rifaximin exposure approximately 12-fold higher than that observed in healthy volunteers following the same dosing regimen. A clinically irrelevant increase of rifaximin systemic absorption was observed when administered within 30 minutes of a high-fat breakfast.

Distribution

Rifaximin is moderately bound to human plasma proteins. *In vivo*, the mean protein binding ratio was 67.5% in healthy subjects and 62% in patients with hepatic impairment when rifaximin 550 mg was administered.

Biotransformation

Analysis of faecal extracts demonstrated that rifaximin is found as the intact molecule, implying that it is neither degraded nor metabolised during its passage through the gastrointestinal tract.

In a study using radio-labelled rifaximin, urinary recovery of rifaximin was 0.025% of the administered dose, while <0.01% of the dose was recovered as 25-desacetylrifaximin, the only rifaximin metabolite that has been identified in humans.

Elimination

A study with radio-labelled rifaximin suggested that ^{14}C-rifaximin is almost exclusively and completely excreted in faeces (96.9 % of the administered dose). The urinary recovery of ^{14}C-rifaximin does not exceed 0.4% of the administered dose.

Linearity/non-linearity

The rate and extent of systemic exposure of humans to rifaximin appeared to be characterized by non-linear (dose-dependent) kinetic which is consistent with the possibility of dissolution-rate-limited absorption of rifaximin.

Special Populations

Renal impairment

No clinical data are available on the use of rifaximin in patients with impaired renal function.

Hepatic impairment

Clinical data available for patients with hepatic impairment showed a systemic exposure higher than that observed in healthy subjects. The systemic exposure of rifaximin was about 10-, 13-, and 20-fold higher in those patients with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, respectively, compared to that in healthy volunteers. The increase in systemic exposure to rifaximin in subjects with hepatic impairment should be interpreted in light of rifaximin gastrointestinal local action and its low systemic bioavailability, as well as the available rifaximin safety data in subjects with cirrhosis.

Therefore no dosage adjustment is recommended because rifaximin is acting locally.

Paediatric population

The pharmacokinetics of rifaximin has not been studied in paediatric patients of any age. Population studied in both the reduction in recurrence of hepatic encephalopathy (HE) and in the acute treatment of HE included patients aged ≥ 18 years.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In a rat embryofetal development study, a slight and transient delay in ossification that did not affect the normal development of the offspring, was observed at 300 mg/kg/day (2.7 times the proposed clinical dose for hepatic encephalopathy, adjusted for body surface area). In the rabbit, following oral administration of rifaximin during gestation, an increase in the incidence of skeletal variations was observed (at doses similar to those proposed clinically for hepatic encephalopathy). The clinical relevance of these findings is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Sodium starch glycolate type A

Glycerol distearate

Colloidal anhydrous silica

Talc

Microcrystalline cellulose

Film coat (opadry oy-s-34907):

Hypromellose

Titanium dioxide (E171)

Disodium edetate

Propylene glycol

Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC-PE-PVDC/Aluminium foil blisters in cartons of 14, 28, 42, 56 or 98 tablets.

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Norgine Pharmaceuticals Ltd

Norgine House,

Widewater Place,

Moorhall Road,

Harefield, Middlesex,

UB9 6NS, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL20011/0020

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/01/2013

10 DATE OF REVISION OF THE TEXT

10/01/2013

10.2 Appendix 2: Search strategy for Section 6.1 (Identification of studies)

The following information should be provided:

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***The Cochrane Library***

The following databases were searched:

- MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
- EMBASE (via Ovid)
- The Cochrane Library (via OVID):
  - The Cochrane Central Register of Controlled Trials (CENTRAL)
  - The Cochrane Database of Systematic Reviews (Cochrane Reviews)
  - The Database of Abstracts of Reviews of Effects (DARE)
  - The Health Technology Assessment Database (HTA)

10.2.2 The date on which the search was conducted

The searches were conducted on 29th May 2012.

10.2.3 The date span of the search

Ovid MEDLINE(R) 1946 to present.

EMBASE (Ovid), 1980 to 2010 Week 36.

The Cochrane Library, to present.

NHS EED (The Cochrane Library), to present.

Econlit (Ovid) 1969 to July 2010.

10.2.4 The complete search strategy used, including all the search terms: textwords (free text), patient index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; Searched on 29th May 2012

#	Searches	Results
1	exp hepatic encephalopathy/	8345
2	((hepatic adj ecephalopathy) or (portosystemic adj encephalopathy) or (hepatic adj coma) or (coma adj hepaticum)).mp.	1722

3	((hepatocerebral or hepatic or cirrho$ or liver) adj10 (encephalopath$ or enzephalopath$ or encefalopat$)).mp.	10980
4	((fulminant or acute) and (liver or hepatic) and failure$1 and cerebral and (edema$2 or oedema$2)).mp.	396
5	or/1-4	11584
6	exp Liver Cirrhosis/	65738
7	(cirrhosis or cirrhoses or cirrhotic or (liver adj failure)).mp.	101280
8	6 or 7	101280
9	5 and 8	5075
10	exp Rifamycins/	16169
11	("rifaximin" or (Rifaximin adj1 alpha) or Rifaximin a or XIFAXANTA or Targaxan).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	515
12	exp Lactulose/	1591
13	exp Disaccharides/	46097
14	exp Sugar Alcohols/	86154
15	(lactulose or disacch* or (sugar adj alcohol*)).mp.	20286
16	exp Neomycin/	8151
17	(neomycin or mycifradin or Neo?Fradin or Neo?Tab).mp.	11565
18	or/10-17	165676
19	9 and 18	382
20	Randomized controlled trials as Topic/	80210
21	Randomized controlled trial/	327847
22	Random allocation/	74365
23	Double blind method/	114775
24	Single blind method/	16135
25	Clinical trial/	469664
26	exp Clinical Trials as Topic/	255277
27	or/20-26	818838
28	(clinic$ adj trial$1).tw.	178463
29	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	116039
30	Placebos/	30887
31	Placebo$.tw.	140920
32	Randomly allocated.tw.	14355
33	(allocated adj2 random).tw.	688
34	or/28-33	362158
35	27 or 34	940929
36	Case report.tw.	178360
37	Letter/	764590
38	Historical article/	282712
39	Review of reported cases.pt.	0

40	Review, multicase.pt.	0
41	or/36-40	1215166
42	35 not 41	914405
43	19 and 42	118

EMBASE 1980 to 2012 Week 21; Searched on 29th May 2012

#	Searches	Results
1	exp hepatic encephalopathy/	10524
2	(((portal adj1 systemi$) or portosystemi$ or subclinical) adj10 (encephalopath$ or enzephalopath$ or encefalopat$)).mp.	1091
3	((hepatocerebral or hepatic or cirrho$ or liver) adj10 (encephalopath$ or enzephalopath$ or encefalopat$)).mp.	13123
4	(hepatic and (coma$1 or stupor$1)).mp.	3179
5	(coma$1 and hepaticum).mp.	101
6	((fulminant or acute) and (liver or hepatic) and failure$1 and cerebral and (edema$2 or oedema$2)).mp.	554
7	or/1-6	14981
8	exp liver cirrhosis/	91626
9	(cirrhosis or cirrhoses or cirrhotic or (liver adj failure)).mp.	134869
10	8 or 9	134869
11	7 and 10	7975
12	exp rifaximin/	1776
13	exp rifamycin/	2317
14	("rifaximin" or (Rifaximin adj1 alpha) or Rifaximin a or XIFAXANTA or Targaxan).mp.	1813
15	exp lactulose/ or exp disaccharide/	58916
16	exp sugar alcohol/	66654
17	(lactulose or disacch* or (sugar adj alcohol*)).mp.	21405
18	exp neomycin/	16423
19	(neomycin or mycifradin or Neo?Fradin or Neo?Tab).mp.	19801
20	or/12-19	150721
21	11 and 20	1102
22	Clinical trial/	865647
23	Randomized controlled trial/	322087
24	Randomization/	58191
25	Single blind procedure/	15895
26	Double blind procedure/	108899
27	Crossover procedure/	33874
28	Placebo/	198544

29	Randomi?ed controlled trial$.tw.	74645
30	Rct.tw.	9196
31	Random allocation.tw.	1137
32	Randomly allocated.tw.	17088
33	Allocated randomly.tw.	1801
34	(allocated adj2 random).tw.	706
35	Single blind$.tw.	12133
36	Double blind$.tw.	127482
37	((treble or triple) adj blind$).tw.	267
38	Placebo$.tw.	174215
39	Prospective study/	203923
40	or/22-39	1245903
41	Case study/	15633
42	Case report.tw.	224649
43	Abstract report/ or letter/	831950
44	or/41-43	1067700
45	40 not 44	1211064
46	21 and 45	313
47	(conference or editorial).pt.	1829890
48	46 not 47	257

The Cochrane Library, to 29th May 2012; Searched on 29th May 2012

EBM Reviews - Cochrane Central Register of Controlled Trials May 2012,
EBM Reviews - Cochrane Database of Systematic Reviews 2005 to May 2012,
EBM Reviews - Database of Abstracts of Reviews of Effects 2nd Quarter 2012,
EBM Reviews - Health Technology Assessment 2nd Quarter 2012

#	Searches	Results
1	exp hepatic encephalopathy/	288
2	((hepatic adj ecephalopathy) or (portosystemic adj encephalopathy) or (hepatic adj coma) or (coma adj hepaticum)).mp.	64
3	((hepatocerebral or hepatic or cirrho$ or liver) adj10 (encephalopath$ or enzephalopath$ or encefalopat$)).mp.	731
4	((fulminant or acute) and (liver or hepatic) and failure$1 and cerebral and (edema$2 or oedema$2)).mp.	32
5	or/1-4	779
6	exp Liver Cirrhosis/	1829
7	(cirrhosis or cirrhoses or cirrhotic or (liver adj failure)).mp.	4720
8	6 or 7	4720
9	5 and 8	505
10	exp Rifamycins/	822

11	("rifaximin" or (Rifaximin adj1 alpha) or Rifaximin a or XIFAXANTA or Targaxan).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	118
12	exp Lactulose/	253
13	exp Disaccharides/	1593
14	exp Sugar Alcohols/	4196
15	(lactulose or disacch* or (sugar adj alcohol*)).mp.	897
16	exp Neomycin/	395
17	(neomycin or mycifradin or Neo?Fradin or Neo?Tab).mp.	554
18	or/10-17	7522
19	9 and 18	127
20	Randomized controlled trials as Topic/	5432
21	Randomized controlled trial/	27
22	Random allocation/	20357
23	Double blind method/	95883
24	Single blind method/	10380
25	Clinical trial/	1
26	exp Clinical Trials as Topic/	39346
27	or/20-26	138025
28	(clinic$ adj trial$1).tw.	51034
29	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	131052
30	Placebos/	20511
31	Placebo$.tw.	125551
32	Randomly allocated.tw.	13185
33	(allocated adj2 random).tw.	1068
34	or/28-33	221101
35	27 or 34	255550
36	Case report.tw.	404
37	Letter/	0
38	Historical article/	0
39	Review of reported cases.pt.	1
40	Review, multicase.pt.	0
41	or/36-40	405
42	35 not 41	255317
43	19 and 42 EBM Reviews - Cochrane Central Register of Controlled Trials <May 2012> (71) EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 2012> (9) EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2012> (1) EBM Reviews - Health Technology Assessment <2nd Quarter 2012> (0)	81

10.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

Hand searching was undertaken as follows:

- Hand-searching of reference lists of included RCTs,
- Hand-searching of RCTs included in relevant recent systematic review publications,
- Hand-searching of conference proceedings. To identify any recent RCTs for which there are currently no full publications, the following conference proceedings between 2010 and 2012 were examined for relevant abstracts:
    - European Association for the Study of the Liver (EASL)
        - The International Liver Congress
        - Monothematic Conference
    - International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN)
    - United European Gastroenterology Week (UEGW)
- The following databases were also accessed, particularly to identify on-going, as yet unpublished, studies:
    - WHO International Clinical Trials Registry Platform (ICTRP)
    - clinicaltrials.gov
    - NCI clinical trial database
    - ISRCTN Register
    - UK Clinical Trials Gateway
    - metaRegister (mRCT) of Controlled Trials

- Unpublished studies (i.e. clinical study reports) from the manufacturer's database.

10.2.6 The inclusion and exclusion criteria.

The inclusion and exclusion criteria can be found in Table 3. A list of excluded studies is provided in Table 72.

Table 72: Studies excluded from the systematic review

	Study Name	Title	Exclusion reason
1	Atterbury, 1978 (94)	Neomycin-sorbitol and lactulose in the treatment of acute portal-systemic encephalopathy. A controlled, double-blind clinical trial	Disease (AHE)
2	Bajaj, 2011 (34)	Rifaximin improves driving simulator performance in a randomized trial of patients with minimal hepatic encephalopathy	Disease (MHE)
3	Basu, 2010 (95)	Transdermal rivastigmine for treatment of encephalopathy in liver cirrhosis - a randomized placebo controlled trial (TREC trial)	Population (no prior episodes stated)

4	Bauer, 2002 (96)	Effects of sorbent suspension dialysis on plasma amino acid levels in cirrhotic patients with refractory hepatic encephalopathy	Population (no prior episodes stated)
5	Blanc, 1994 (97)	Lactulose-neomycin combination versus placebo in the treatment of acute hepatic encephalopathy. Results of a randomized controlled trial. [French]	Population (no prior episodes stated)
6	Bucci, 1993 (90)	Double-blind, double-dummy comparison between treatment with rifaximin and lactulose in patients with medium to severe degree hepatic encephalopathy	Population (no prior episodes stated)
7	Cerra, 1983 (98)	Cirrhosis, encephalopathy, and improved results with metabolic support	Population (no prior episodes stated)
8	Cerra, 1985 (99)	Disease-specific amino acid infusion (F080) in hepatic encephalopathy: A prospective, randomized, double-blind, controlled trial	Population (no prior episodes stated)
9	Chesta, 1994 (100)	Effects of neomycin on intestinal digestion, absorption and fermentation of carbohydrates in patients with liver cirrhosis: evidence for an alternative therapeutic mechanism in hepatic encephalopathy. [Spanish]	Not relevant disease
10	Conn, 1977 (101)	Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial	Population (prior episodes in only uncertain percentage)
11	Dhiman, 2000 (102)	Efficacy of lactulose in cirrhotic patients with subclinical hepatic encephalopathy	Disease
12	Di Piazza, 1991 (103)	Rifaximine versus neomycin in the treatment of portosystemic encephalopathy	Study design (no randomisation reported)
13	Festi, 1993 (91)	Rifaximin in the treatment of chronic hepatic encephalopathy; resultes of a multicenter study of efficacy and safety	Population (no prior episodes stated)
14	Germain, 1973 (104)	Double blind study of lactulose in 8 patients with chronic hepatic encephalopathy after portocaval shunt. [French]	Study design; No randomisation reported; Foreign language
15	Grandi, 1991 (105)	A clinical comparative study of crystalline pure lactulose and powder pure lactitol in portasystemic encephalopathy of cirrhotic patients. [Italian]	Study design; No randomisation reported; Foreign language
16	Hassanein, 2007 (106)	Randomized controlled study of extracorporeal albumin dialysis for hepatic encephalopathy in advanced cirrhosis	Population (no prior episodes stated)
17	Heredia, 1987 (107)	Lactitol versus lactulose in the treatment of acute portal systemic encephalopathy (PSE). A controlled trial	Disease
18	Horsmans, 1997 (108)	Lactulose improves psychometric testing in cirrhotic patients with subclinical encephalopathy	Disease
19	Jalan, 2010 (109)	Rifaximin in hepatic encephalopathy: More than just a non-absorbable antibiotic?	Comment; Study Design
20	Jankovic, 1996 (110)	Lactitol in the treatment of acute hepatic encephalopathy in liver cirrhosis	Disease
21	Hawley K, 1986 (111)	Randomised controlled double blind trial of lactitol and lactulose in acute hepatic encephalopathy in cirrhotic patients	Disease

		[abstract]	
22	Hawley KE, 1986 (112)	Lactitol vs lactulose in the treatment of acute hepatic encephalopathy in cirrhotic patients: a double-blind randomised trial [AASLD abstract]	Disease
23	Hawley KE, 1986 (113)	A randomised controlled double-blind trial of lactitol and lactulose in acute hepatic encephalopathy in cirrhotic patients [EASL abstract]	Disease
24	Laccetti, 2000 (114)	Flumazenil in the treatment of acute hepatic encephalopathy in cirrhotic patients: A double blind randomized placebo controlled study	Not relevant treatment
25	Loguercio, 1987 (115)	Enterococcus lactic acid bacteria strain SF68 and lactulose in hepatic encephalopathy: A controlled study	Disease
26	Malaguarnera, 2010 (116)	Bifidobacterium combined with fructo-oligosaccharide versus lactulose in the treatment of patients with hepatic encephalopathy	Population (no prior episodes stated)
27	Mas, 2003 (92)	Comparison of rifaximin and lactitol in the treatment of acute hepatic encephalopathy: Results of a randomized, double-blind, double-dummy, controlled clinical trial	Disease
28	Miglio, 1997 (93)	Rifaximin, a non-absorbable rifamycin, for the treatment of hepatic encephalopathy. A double-blind, randomised trial	Population (no prior episodes stated)
29	Mittal, 2011 (117)	A randomized controlled trial comparing lactulose, probiotics, and L-ornithine L-aspartate in treatment of minimal hepatic encephalopathy	Disease
30	Morgan, 1987 (118)	Lactitol vs. lactulose in the treatment of acute hepatic encephalopathy in cirrhotic patients: A double-blind, randomized trial	Disease
31	Morgan, 1987 (119)	Lactitol versus lactulose in the treatment of chronic hepatic encephalopathy. A double-blind, randomised, cross-over study	Population (no prior episodes stated)
32	Morgan, 1989 (120)	Lactitol and lactulose for the treatment of subclinical hepatic encephalopathy in cirrhotic patients. A randomised, cross-over study	Disease
33	Mullen, 2010 (1)	Rifaximin for the treatment of hepatic encephalopathy.[Erratum appears in Expert Rev Gastroenterol Hepatol. 2011 Feb;5(1):133-4]	Study design; Review
34	Orlandi, 1981 (121)	Comparison between neomycin and lactulose in 173 patients with hepatic encephalopathy. A randomized clinical study	Population (no prior episodes stated)
35	Pai, 1995 (122)	Treatment of porto-systemic encephalopathy with lactitol versus lactulose: A randomized controlled study	Population (no prior episodes stated)
36	Parini, 1992 (123)	Effect of rifaximin and paromomycin in the treatment of portal-systemic encephalopathy	Population (no prior episodes stated)
37	Pedretti, 1991 (124)	Rifaximin versus neomycin on hyperammoniemia in chronic portal systemic encephalopathy of cirrhotics. A double-blind, randomized trial	Population (prior episodes in only 63%)

38	Di Piazza, 1991 (103)	Rifaximine versus neomycin in the treatment of portosystemic encephalopathy	Study design (no randomisation reported)
39	Prasad, 2007 (125)	Lactulose improves cognitive functions and health-related quality of life in patients with cirrhosis who have minimal hepatic encephalopathy	Disease
40	Riggio, 1990 (126)	Lactitol in the treatment of chronic hepatic encephalopathy - A randomized cross-over comparison with lactulose	Population (prior episodes in only 71%)
41	Riggio, 2005 (127)	Pharmacological prophylaxis of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt: A randomized controlled study	Population; Prophylaxis of HE; Patients don't have HE when entered
42	Russo, 1989 (128)	Ribostamycin for the treatment of hepatic encephalopathy: A crossover study with lactulose	Population (no prior episodes stated)
43	Sharma, 2008 (129)	An open-label randomized controlled trial of lactulose and probiotics in the treatment of minimal hepatic encephalopathy	Disease
44	Sharma, 2011 (130)	Prophylaxis of hepatic encephalopathy in acute variceal bleed: A randomized controlled trial of lactulose versus no lactulose	Study design; Prophylaxis of HE; Patients don't have HE when entered
45	Siddique, 2010 (131)	Gut instinct: Rifaximin for the prevention of hepatic encephalopathy	Comment; Study Design
46	Sidhu, 2011 (132)	Rifaximin improves psychometric performance and health-related quality of life in patients with minimal hepatic encephalopathy (the RIME trial)	Disease
47	Strauss, 1992 (133)	Double-blind randomized clinical trial comparing neomycin and placebo in the treatment of exogenous hepatic encephalopathy	Disease
48	Sushma, 1992 (134)	Sodium benzoate in the treatment of acute hepatic encephalopathy: A double-blind randomized trial	Disease
49	Szalay, 2004 (135)	Rifaximin in the treatment of hepatic encephalopathy - A multicentric study. [Hungarian]	Study design; No randomisation reported; Foreign language
50	Uribe, 1980 (136)	Treatment of chronic portal-systemic encephalopathy with lactose in lactase-deficient patients	Study design; Randomisation not reported
51	Uribe, 1987 (137)	Lactitol, a second-generation disaccharide for treatment of chronic portal-systemic encephalopathy. A double-blind, crossover, randomized clinical trial	Population (no prior episodes stated)
52	Venturini, 2005 (138)	Evaluation of rifaximin, placebo and lactulose in reducing the levels of benzodiazepine-like compounds in patients with liver cirrhosis: A pilot study	Study design; Pilot study; Patients were not with HE when entered
53	Vilstrup, 1990 (139)	Branched chain enriched amino acid versus glucose treatment of hepatic encephalopathy. A double-blind study of 65 patients with cirrhosis	Intervention; Not relevant treatment

54	Williams, 2000 (140)	Evaluation of the efficacy and safety of rifaximin in the treatment of hepatic encephalopathy: A double-blind randomized, dose-finding multi-centre study	Study design; Dose finding study

10.2.7 The data abstraction strategy.

Identified studies were independently assessed by two reviewers in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party. Relevant information was abstracted into the STA template/ into a pre-defined Microsoft Word® document by a reviewer. A second reviewer checked the data extraction and any inconsistencies were resolved through discussion.

10.3 Appendix 3: Quality assessment of RCT(s) (Section 6.4)

10.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Quality assessment of the pivotal RCT for rifaximin, Bass et al, (22)

Study RFHE3001		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Was randomisation carried out appropriately?	Patients were randomly assigned in a 1:1 ratio with the computer-generated randomisation schedule	Yes
Was the concealment of treatment allocation adequate?	Bottles of study medication were labelled with the investigational use statement, protocol number, treatment (bottle) number, lot number and manufacturing date or expiration date, quantity, dosing instructions, storage information, and sponsor's name and address. Lactulose containers were labelled with the investigational use statement, protocol number, lot number and expiration date, dosing instructions, storage information, and the manufacturer's name and address.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	No. of HE episodes in the past 6 months were 2 in 69.3% with rifaximin group and 69.8% with comparator group; Conn score during most recent HE episode before study was 2 in 82.1% with rifaximin and 81.8% with comparator group, Conn score of 3 or 4 was in 16.4% with rifaximin and comparator group alike.	Yes

Study RFHE3001		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	In order to facilitate blinding of subjects and study site personnel (double-blind), both placebo and active treatment were identical in appearance	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	52 discontinued from the rifaximin group and 93 discontinued from comparator group, with primary reason being breakthrough HE. But all assigned patients were included in the efficacy and safety population (ITT)	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All measured outcomes were reported	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

10.4 Appendix 4: Search strategy for Section 6.7 (Indirect and mixed treatment comparisons)

The clinical search described in Section 6.1 and Section 10.2 was designed to identify eligible studies for comparator interventions, relevant to the decision problem.

The following information should be provided:

10.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- ***Medline***
- ***Embase***
- ***Medline (R) in-Process***
- ***The Cochrane Library***

See Section 6.1 and Section 10.2

10.4.2 The date on which the search was conducted

See Section 6.1 and Section 10.2

10.4.3 The date span of the search

See Section 6.1 and Section 10.2

10.4.4 The complete search strategies used. including all the search terms: textwords (free text), patient index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See Section 6.1 and Section 10.2

10.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

See Section 6.1 and Section 10.2

10.4.6 The inclusion and exclusion criteria.

See Section 6.1 and Section 10.2

10.4.7 The data abstraction strategy.

See Section 6.1 and Section 10.2

10.5 Appendix 5: Quality assessment of comparator RCT(s) in Section 6.7 (Indirect and mixed treatment comparisons)

10.5.1 A suggested format for the quality assessment of RCT(s) is shown below.

No relevant studies were identified for inclusion in an indirect or mixed treatment comparison.

10.6 Appendix 6: Search strategy for Section 6.8 (Non-RCT evidence)

A systematic literature search was not undertaken for non-RCT evidence. Only one rifaximin non-RCT in the patient population of interest has been conducted (RFHE3002, open-label extension phase of the pivotal study (RFHE3001).

10.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***The Cochrane Library***

N/A

10.6.2 The date on which the search was conducted.

N/A

10.6.3 The date span of the search.

N/A

10.6.4 The complete search strategies used. including all the search terms: textwords (free text), patient index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

N/A

10.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

N/A

10.6.6 The inclusion and exclusion criteria.

N/A

10.6.7 The data abstraction strategy.

N/A

10.7 Appendix 7: Quality assessment of non-RCT(s) in Section 6.8 (Non-RCT evidence)

10.7.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Only one-non RCT was identified relevant to the decision problem, RFHE3002 (45). The quality assessment of this study is outlined in Table 73. The quality assessment was completed using criteria outlined by Chambers et al 2009 (141).

Table 73: Quality assessment of RFHE3002

Study	RFHE3002
Eligibility criteria adequately reported?	Yes
Study population representative of a normal population?	Yes
An appropriate measure of variability reported?	Yes
Loss to follow-up reported or explained?	Yes
At least 90% included at baseline followed-up?	Yes
Were patients recruited prospectively?	Yes
Were patients recruited consecutively?	Yes
Did the study report relevant prognostic factors?	Yes
Quality score†	**Good**

† Good, if the answer is ‘‘yes’’ to all of criteria 1-8; satisfactory, if the answer is ‘‘yes’’ to criteria 2, 4-7; poor, if the answer is not ‘‘yes’’ to one or more of the criteria listed for ‘‘satisfactory.’’

Abbreviations: CSR, Clinical Study Report; OLE, Open-label extension

10.8 Appendix 8: Search strategy for Section 6.9 (Adverse events)

The clinical search described in Section 6.1 and Section 10.2 was also designed to identify eligible studies for the adverse events associated with rifaximin.

10.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***The Cochrane Library***

N/A

10.8.2 The date on which the search was conducted.

N/A

10.8.3 The date span of the search.

N/A

10.8.4 The complete search strategies used including all the search terms: textwords (free text), patient index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

N/A

10.8.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

N/A

10.8.6 The inclusion and exclusion criteria.

N/A

10.8.7 The data abstraction strategy.

N/A

10.9 Appendix 9: Quality assessment of adverse event data in Section 6.9 (Adverse events)

10.9.1 Please tabulate the quality assessment of each of studies identified.

A quality assessment of relevant studies can be found in Section 10.3

10.10 Appendix 10: Search strategy for cost-effectiveness studies (Section 7.1)

10.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***NHS EED***
- ***EconLIT***

MEDLINE and EMBASE were searched using Elsevier's Embase Biomedical Answers Web site (combines Embase and MEDLINE content into a single, Web-accessible platform (http://www.embase.com), with duplicate citations removed

Wiley online website: The Cochrane Library, NHS Economic Evaluation Database (NHS-EED, as part of The Cochrane Library)

10.10.2 The date on which the search was conducted.

12th May 2011

10.10.3 The date span of the search.

Embase records from 1974 to present

Medline records from 1950 to present

The Cochrane Library 2011 Issue 5 (CDSR) and Issue 2 (CENTRAL and other databases)

10.10.4 The complete search strategies used, including all the search term textwords (free text), patient index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The following terms were used for the Embase + MEDLINE search:

P: Patient, Population, Problem terms

Relevant search terms comprising indexed keywords (subject headings) and free text terms appearing in titles and/or abstracts of records were used to identify the target indication, being hepatic encephalopathy terms.

1 "hepatic encephalopathy"/de

((hepatic OR hepato OR hepatogenous OR Hepatocerebral OR liver OR ammoniac OR

2 "porta cava" OR portacaval OR portal OR portocaval OR Portosystemic) NEAR/2 encephalopath*):ab,ti

3 ("hepato cerebral disease" OR "hepatocerebral disease" OR "hepatocerebral syndrome" OR hepatoencephalopathy OR "Hepatic Coma" OR "Hepatic Stupor"):ti,ab

I: Intervention terms

Relevant search terms comprising indexed keywords (subject headings) and free text terms appearing in titles and/or abstracts of records were used to filter the search retrieval to the intervention of interest, being rifaximin terms.

5 rifaximin/de

(rifaximin OR xifaxan OR flonorm OR "I 105" OR lumenax OR normix OR redactiv OR

6 rifaxidin):tn,ti,ab

7 (80621-81-4 OR 88747-56-2):rn

Study Type filter terms

Relevant search terms comprising indexed keywords (subject headings) and free text terms appearing in titles and/or abstracts of records were used to filter the search retrieval to economic evaluations, cost-effectiveness, cost-utility and cost-benefit.

This strategy was modified and repeated in The Cochrane Library databases. Slight changes were required to the syntax of the search, which is dependent upon the search platform used and to accommodate indexing differences in the databases. This search was not limited by date and there were no database restrictions.

Embase.com search, *<1966 to 12 May 2011 (*)*

Embase Session Results

No.	Query	Results
#15	**#9** AND **#14**	**47**
#14	**#10** OR **#11** OR **#12** OR **#13**	**831976**
#13	**cost**:de,ab,ti OR **costs**:de,ab,ti OR **costed**:de,ab,ti OR **costly**:de,ab,ti OR **costing**:de,ab,ti OR **economic***:de,ab,ti OR **pharmacoeconomic***:de,ab,ti	**753377**
#12	**'pharmacoeconomics'**/exp	**134731**
#11	**'health care cost'**/exp	**160559**
#10	**'economic evaluation'**/exp	**166541**
#9	**#4** AND **#8**	**270**
#8	**#5** OR **#6** OR **#7**	**1617**
#7	**'80621 81 4'**:rn OR **'88747 56 2'**:rn	**1402**
#6	**rifaximin**:tn,ab,ti OR **xifaxan**:tn,ab,ti OR **flonorm**:tn,ab,ti OR **'I 105'**:tn,ab,ti OR **lumenax**:tn,ab,ti OR **normix**:tn,ab,ti OR **redactiv**:tn,ab,ti OR **rifaxidin**:tn,ab,ti	**826**
#5	**'rifaximin'**/de	**1485**
#4	**#1** OR **#2** OR **#3**	**12613**
#3	**'hepato cerebral disease'**:ab,ti OR **'hepatocerebral disease'**:ab,ti OR **'hepatocerebral syndrome'**:ab,ti OR **hepatoencephalopathy**:ab,ti OR **'hepatic coma'**:ab,ti OR **'hepatic stupor'**:ab,ti	**1951**
#2	((**hepatic** OR **hepato** OR **hepatogenous** OR **hepatocerebral** OR **liver** OR **ammoniac** OR **'porta cava'** OR **portacaval** OR **portal** OR **portocaval** OR **portosystemic**) NEAR/2 **encephalopath***):ab,ti	**6542**
#1	**'hepatic encephalopathy'**/de	**9934**

* The search was conducted using Elesvier's Embase Biomedical Answers Web site on 13 May 2011.

The Cochrane Library search, 2011 Issue 5 (CDSR) and Issue 2 (CENTRAL and the other databases) (*)

Current Search History

ID Search	Hits
#1 MeSH descriptor **Hepatic Encephalopathy**, this term only	301
((hepatic OR hepato OR hepatogenous OR Hepatocerebral OR liver OR	
#2 ammoniac OR "porta cava" OR portacaval OR portal OR portocaval OR Portosystemic) NEAR/2 encephalopath*):ab,ti,kw	614
("hepato cerebral disease" OR "hepatocerebral disease" OR "hepatocerebral	
#3 syndrome" OR hepatoencephalopathy OR "Hepatic Coma" OR "Hepatic Stupor"):ti,ab,kw	35
#4 (#1 OR #2 OR #3)	634
#5 MeSH descriptor **Rifamycins**, this term only	94
#6 (rifaximin OR xifaxan OR flonorm OR "l 105" OR lumenax OR normix OR redactiv OR rifaxidin):kw,ti,ab	105
#7 (#5 OR #6)	138
#8 (#4 AND #7)	36
#9 (#8) in NHS Economic Evaluation Database	3
#10 (#8) in Health Technology Assessment Database	0
#11 MeSH descriptor **Costs and Cost Analysis** explode all trees	31609
#12 (cost or costs or costed OR costly OR costing OR economic* OR	50072
pharmacoeconomic*):ti,ab,kw	
#13 (#11 OR #12)	50096
#14 (#8 AND #13)	4
#15 (#9 OR #10 OR #14)	4

* The search was conducted using Wiley Online on 13 May 2011.

Breakdown of database retrieval from the Cochrane Library

2011 Issue 5 (CDSR) and Issue 2 (CENTRAL and the other databases)

Database	Results
Cochrane Database of Systematic Reviews (CDSR)	0
Database of Abstracts of Reviews of Effects (DARE)	0
Cochrane Central Register of Controlled Trials (CENTRAL)	1
Cochrane Methodology Register (CMR)	0
Health Technology Assessment Database (HTA)	0

NHS Economic Evaluation Database (NHSEED)	3
Cochrane Groups	0
Total	**4**

10.10.5 Details of any additional searches, (for example, searches of company databases [include a description of each database]).

A review of health technology assessment websites was conducted in May 2011 to identify economic evaluations of rifaximin for the prevention of HE. The websites searched, along with the search terms used and the number of articles found, are shown in Table 74.

Table 74: Search of health technology websites

Organisation	Search Strings (articles found)	Relevant Documents
Canadian Agency for Drugs and Technologies in Health http://www.cadth.ca/en	Rifaximin = 0	0
Pharmacology and Therapeutics Advisory Committee (Pharmac: Pharmaceutical Management Agency) http://www.pharmac.govt.nz/ptac.asp	Rifaximin = 0	0
Scottish Medicine Consortium www.scottishmedicines.org.uk	Rifaximin = 0	0
National Institute of Health and Clinical Excellence www.nice.org.uk	Rifaximin = 1	0
Centre for Reviews and Dissemination (encompassing the Database of Abstracts of Reviews of Effects – DARE, the NHS Economic Evaluation Database – NHS EED, and the Health Technology Assessment Database – HTA) http://www.crd.york.ac.uk/CRDWeb/Home.aspx	Rifaximin or hepatic encephalopathy = 56.	1

There were no relevant hits from the websites of the HTA agencies.

10.10.6 The inclusion and exclusion criteria.

Papers were excluded for further review for the following reasons:

A. did not refer to HE;

B. did not report the results of an economic evaluation (only cost-analyses, were not incremental, or were reviews of HRQoL only); or
C. review, including reviews of economic evaluations published elsewhere.

10.10.7 The data abstraction strategy.

Not reported.

10.11 Appendix 11: Quality assessment of cost-effectiveness studies (Section 7.1)

Quality assessment was not undertaken.

10.12 Appendix 12: Search strategy for Section 7.4 (Measurement and valuation of health effects)

10.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***NHS EED***
- ***EconLIT***

MEDLINE and EMBASE were searched using Elsevier's Embase Biomedical Answers Web site (combines Embase and MEDLINE content into a single, Web-accessible platform (http://www.embase.com), with duplicate citations removed

Wiley online website: The Cochrane Library, NHS Economic Evaluation Database (NHS-EED, as part of The Cochrane Library)

10.12.2 The date on which the search was conducted.

Original search was conducted in May 2011. This was updated in February 2012 using PubMed with the following search terms: "hepatic encephalopathy" AND "(utility weight) OR (utility value) OR (preference weight) OR (quality of life weight)", and limited to publications from 1 May 2011 onwardsResponse]

10.12.3 The date span of the search.

Embase records from 1974 to present

Medline records from 1950 to present

The Cochrane Library 2011 Issue 5 (CDSR) and Issue 2 (CENTRAL and other databases)

10.12.4 The complete search strategies used, including all the search terms textwords (free text), patient index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The following terms were used for the Embase + MEDLINE search:

P: Patient, Population, Problem terms

Relevant search terms comprising indexed keywords (subject headings) and free text terms appearing in titles and/or abstracts of records were used to identify the target indication, being hepatic encephalopathy terms.

1 "hepatic encephalopathy"/de

((hepatic OR hepato OR hepatogenous OR Hepatocerebral OR liver OR ammoniac OR

2 "porta cava" OR portacaval OR portal OR portocaval OR Portosystemic) NEAR/2 encephalopath*):ab,ti

3 ("hepato cerebral disease" OR "hepatocerebral disease" OR "hepatocerebral syndrome" OR hepatoencephalopathy OR "Hepatic Coma" OR "Hepatic Stupor"):ti,ab

I: Intervention terms

Relevant search terms comprising indexed keywords (subject headings) and free text terms appearing in titles and/or abstracts of records were used to filter the search retrieval to the intervention of interest, being rifaximin terms.

5 rifaximin/de

(rifaximin OR xifaxan OR flonorm OR "l 105" OR lumenax OR normix OR redactiv OR

6 rifaxidin):tn,ti,ab

7 (80621-81-4 OR 88747-56-2):rn

Study Type filter terms

Relevant search terms comprising indexed keywords (subject headings) and free text terms appearing in titles and/or abstracts of records were used to filter the search retrieval to economic evaluations, cost-effectiveness, cost-utility and cost-benefit.

This strategy was modified and repeated in The Cochrane Library databases. Slight changes were required to the syntax of the search, which is dependent upon the search platform used and to accommodate indexing differences in the databases. This search was not limited by date and there were no database restrictions.

Embase.com search, <1966 to 12 May 2011 (*)

Embase Session Results

No.	Query	Results
#39	**#10** OR **#38**	**70**
#38	**#4** AND **#37**	**51**
#37	**#11** OR **#16** OR **#17** OR **#18** OR **#19** OR **#20** OR **#21** OR **#22** OR **#23** OR **#24** OR **#25** OR **#26** OR **#27** OR **#28** OR **#29** OR **#30** OR **#31** OR **#32** OR **#33** OR **#34** OR **#35** OR **#36**	**54712**
#36	**'time tradeoff'**:de,ab,ti OR **'time trade off'**:de,ab,ti OR **tto**:de,ab,ti	**1057**
#35	**'stated preference'**:de,ab,ti OR **'stated preferences'**:de,ab,ti	**235**
#34	**'standard gamble'**:ab,ti OR **sg**:ab,ti	**5584**
#33	**'standard gamble'**:de	**26**
#32	**mau**:ab,ti OR **mau?**:ab,ti	**6319**
#31	**'multi attribute utility'**:de,ab,ti OR **'multiattribute utility'**:de,ab,ti	**182**
#30	(**health** NEXT/2 (**utilities** OR **utility**)):ab,ti OR **hui**:ab,ti OR **hui?**:ab,ti	**5946**
#29	**'health state utility'**:de OR **'health utility index'**:de OR **'utilities index'**:de	**89**
#28	**'health quality'**:ab,ti OR **'health related quality'**:ab,ti OR **hrqol**:ab,ti	**18749**
#27	**15d**:ab,ti OR **'15 d'**:ab,ti	**3205**

#26	**'eq 5d'**:ab,ti OR **eq5d**:ab,ti OR **euroqol**:ab,ti OR **'european quality of life'**:ab,ti	**3149**
#25	**'european quality of life'**:de	**113**
#24	**'euroqol 5d'**:de OR **'eq 5d'**:de OR **'eq 5d scale'**:de	**122**
#23	**'discrete choice'**:de,ab,ti OR **'discrete choices'**:de,ab,ti OR **'choice experiment'**:de,ab,ti OR **'choice experiments'**:de,ab,ti	**897**
#22	**'australian qol'**:ab,ti OR **'australian quality of life'**:ab,ti	**4**
#21	**aqol**:de,ab,ti OR **'assessment of quality of life'**:de,ab,ti	**1053**
#20	**'quality of life index'**:ab,ti	**1050**
#19	**'quality of life index'**/de	**776**
#18	**qaly***:ab,ti OR **daly***:ab,ti OR **'adjusted life'**:ab,ti	**7268**
#17	**'quality adjusted'**:de,ab,ti OR **'disability adjusted'**:de,ab,ti	**9799**
#16	**#14** AND **#15**	**838**
#15	**'life expectancy'**/exp	**21663**
#14	**#12** OR **#13**	**92939**
#13	**'disabled person'**/exp	**21423**
#12	**'disability'**/exp	**73334**
#11	**'quality adjusted life year'**/exp	**7250**
#10	**#4** AND **#9**	**23**
#9	**#5** OR **#6** OR **#7** OR **#8**	**159470**
#8	**preference***:ab,ti	**81233**
#7	(**utility** NEXT/1 (**value*** OR **weight***)):ab,ti	**739**
#6	(**health** NEXT/1 (**status** OR **state** OR **states**)):ab,ti	**35731**
#5	**'health status'**/de	**63865**
#4	**#1** OR **#2** OR **#3**	**12613**
#3	**'hepato cerebral disease'**:ab,ti OR **'hepatocerebral disease'**:ab,ti OR **'hepatocerebral syndrome'**:ab,ti OR **hepatoencephalopathy**:ab,ti OR **'hepatic coma'**:ab,ti OR **'hepatic stupor'**:ab,ti	**1951**
#2	((**hepatic** OR **hepato** OR **hepatogenous** OR **hepatocerebral** OR **liver** OR **ammoniac** OR **'porta cava'** OR **portacaval** OR **portal** OR **portocaval** OR **portosystemic**) NEAR/2 **encephalopath***):ab,ti	**6542**
#1	**'hepatic encephalopathy'**/de	**9934**

* The search was conducted using Elesvier's Embase Biomedical Answers Web site on 13 May 2011.

The Cochrane Library search,

2011 Issue 5 (CDSR) and Issue 2 (CENTRAL and the other databases) (*)

Current Search History

ID Search	Hits
#1 MeSH descriptor **Hepatic Encephalopathy**, this term only	301
#2 ((hepatic OR hepato OR hepatogenous OR Hepatocerebral OR liver OR ammoniac OR "porta cava" OR portacaval OR portal OR portocaval OR Portosystemic) NEAR/2 encephalopath*):ab,ti,kw	614
#3 ("hepato cerebral disease" OR "hepatocerebral disease" OR "hepatocerebral syndrome" OR hepatoencephalopathy OR "Hepatic Coma" OR "Hepatic Stupor"):ti,ab,kw	35
#4 (#1 OR #2 OR #3)	634
#5 MeSH descriptor **Health Status**, this term only	2637
#6 (Health NEAR/1 (Status OR state OR states)):ti,ab,kw	5417
#7 (utility NEAR/1 (value* OR weight*)):ti,ab,kw	63
#8 preference*:ti,ab,kw	5010
#9 (#5 OR #6 OR #7 OR #8)	10235
#10 (#4 AND #9)	5
#11 MeSH descriptor **Quality-Adjusted Life Years**, this term only	2995
#12 ("quality adjusted" or "disability adjusted"):ti,ab,kw	3381
#13 (qaly* or daly* or "adjusted life"):ti,ab,kw	3369
#14 (aqol or "assessment of quality of life"):ti,ab,kw	135
#15 ("australian qol" OR "australian quality of life"):ti,ab,kw	1
#16 ("discrete choice" OR "discrete choices" OR "choice experiment" OR "choice experiments"):ti,ab,kw	64
#17 ("eq 5d" or eq5d or euroqol OR "european quality of life"):ti,ab,kw	631
#18 (15d or "15 d"):ti,ab,kw	146
#19 ("health quality" or "health related quality" or hrqol):ti,ab,kw	2910
#20 ((Health NEAR/2 (Utilities OR utility)) or hui OR hui?):ti,ab,kw	219
#21 ("Multi attribute utility" OR "Multiattribute utility"):ti,ab,kw	9
#22 (mau OR Mau?):ti,ab,kw	14
#23 ("standard gamble" or sg):ti,ab,kw	306
#24 ("stated preference" OR "stated preferences"):ti,ab,kw	27

#25 ("time tradeoff" or "time trade off" or tto):ti,ab,kw	126
#26 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25)	7244
#27 (#4 AND #26)	5
#28 (#10 OR #27)	10

* The search was conducted using Wiley Online on 13 May 2011.

Breakdown of database retrieval from The Cochrane Library,

2011 Issue 5 (CDSR) and Issue 2 (CENTRAL and the other databases)

Database	Results
Cochrane Database of Systematic Reviews (CDSR)	0
Database of Abstracts of Reviews of Effects (DARE)	0
Cochrane Central Register of Controlled Trials (CENTRAL)	10
Cochrane Methodology Register (CMR)	0
Health Technology Assessment Database (HTA)	0
NHS Economic Evaluation Database (NHSEED)	0
Cochrane Groups	0
Total	**10**

10.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

N/A.

10.12.6 The inclusion and exclusion criteria.

Citations were excluded from further review if they:

A. were not reporting on HE;
B. were QoL studies that did not report preference based utility weights (publications which were based on transformations of HRQoL instruments to utilities were excluded), or did not report utility values; or
C. were not a QoL study.

10.12.7 The data abstraction strategy.

Not reported.

10.13 Appendix 13: Resource identification, measurement and valuation (Section 7.5)

N/A. A systematic review was not conducted to identify resource data from the published literature. Resource use (outpatient visits and hospitalisations) was identified via clinical opinion.

10.13.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

N/A

10.13.2 The date on which the search was conducted.

N/A

10.13.3 The date span of the search.

N/A

10.13.4 The complete search strategies used, including all the search terms textwords (free text), patient index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

N/A

10.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

N/A

10.13.6 The inclusion and exclusion criteria.

N/A

10.13.7 The data abstraction strategy.

N/A