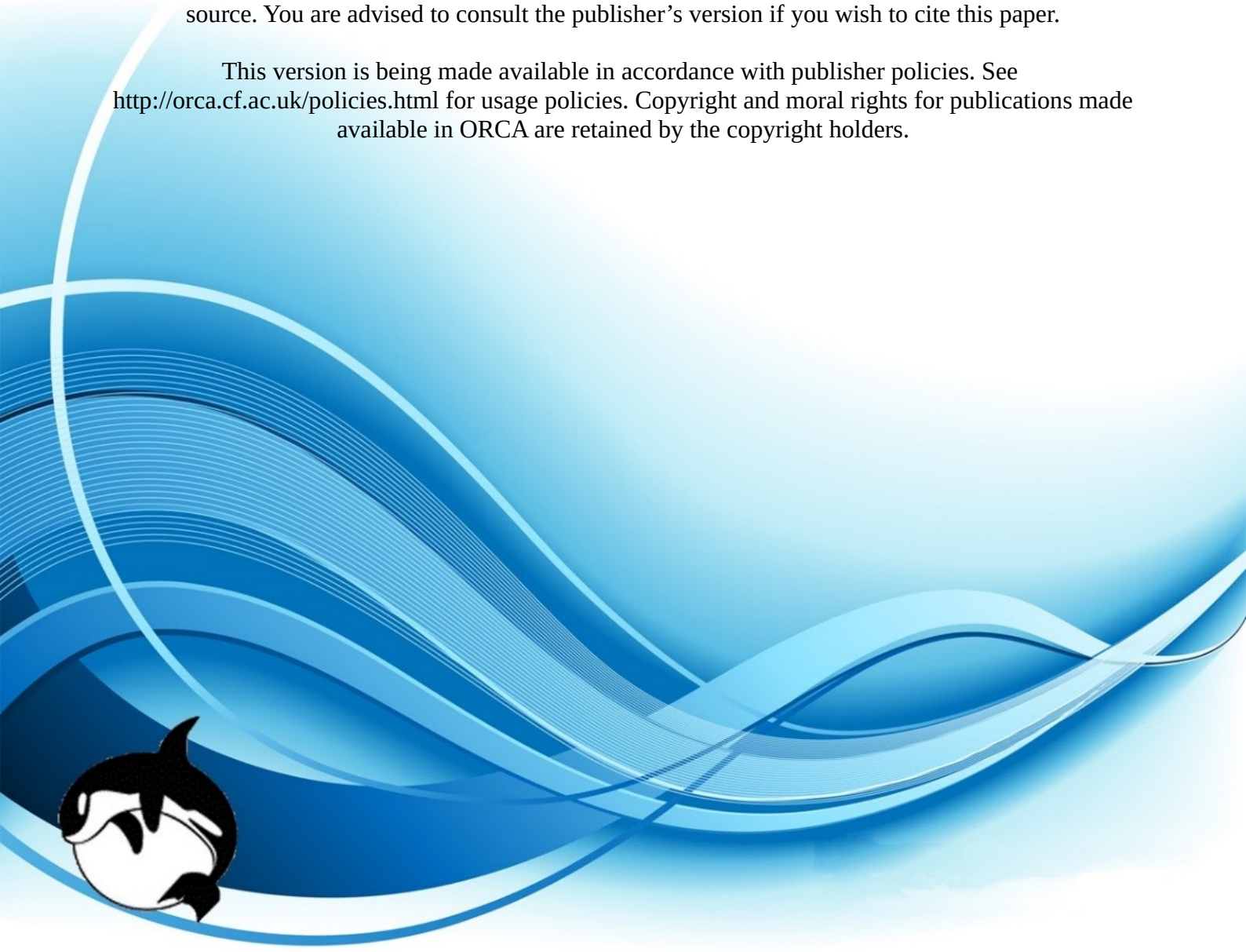

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Evaluation of the cost-effectiveness of rifaximin-α for the management of patients with hepatic encephalopathy in the United Kingdom

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Transparency section

Declaration of financial and other interest

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Declaration of financial and other interest

DM, JW and PDM are employees of Norgine Pharmaceuticals Limited who hold the marketing authorization for rifaximin-α in the United Kingdom. PC, EB, CC and CP provided consulting services and manuscript preparation services to Norgine Pharmaceuticals Limited. A CMRO peer reviewer on this manuscript was the principal investigator of a pivotal study cited by the authors as a major source document for their analysis. All other peer reviewers have no other disclosures.

Author contribution

JW, EB, CC and PC have contributed to the conception and design of the analysis. All authors contributed to drafting and revising the manuscript and gave final approval of the publication version.

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None reported.

Abstract

Objective

Rifaximin-α 550 mg twice daily plus lactulose has demonstrated efficacy in reducing recurrence of episodes of overt HE (OHE) and the risk of HE-related hospitalisations compared with lactulose alone. This analysis estimated the cost effectiveness of rifaximin-α 550 mg twice daily plus lactulose versus lactulose alone in UK cirrhotic patients with OHE.

Method

A Markov model was built to estimate the incremental cost effectiveness ratio (ICER). The perspective was that of the UK National Health Service (NHS). Clinical data were sourced from a randomised controlled trial (RCT) and an open-label maintenance (OLM) study in cirrhotic patients in remission from recurrent episodes of OHE. Health-related utility was estimated indirectly from disease-specific quality of life RCT data. Resource use data describing the impact of rifaximin-α on hospital admissions and length of stay for cirrhotic patients with OHE were from four single-centre UK audits. Costs (2012) were derived from published sources; costs and benefits were discounted at 3.5%. The base-case time horizon was five years.

Results

The average cost per patient was £22,971 in the rifaximin-α plus lactulose arm and £23,545 in the lactulose arm, a saving of £573. The corresponding values for benefit were 2.35 QALYs and 1.83 QALYs per person, a difference of 0.52 QALYs. This translated into a dominant base-case ICER. Key parameters that impacted the ICER included number of hospital admissions and length of stay.

Conclusion

Rifaximin-α 550 mg twice daily in patients with recurrent episodes of overt HE was estimated to generate cost savings and improved clinical outcomes compared to standard care over five years.

Keywords: Hepatic Encephalopathy, Rifaximin, Cost-Utility Analysis, Cost-Benefit Analysis

Introduction

Liver cirrhosis is a progressive condition associated with high morbidity and mortality. It occurs over a period of years in response to liver damage following exposure to one or more risk factors such as alcohol misuse, non-alcoholic fat liver deposition and viral infections [1]. The occurrence of complications in cirrhotic patients alters the natural history of liver disease, resulting in a poorer prognosis, greater hospital management and increased mortality [2]. One of the major complications of cirrhosis and most debilitating manifestations of liver disease is hepatic encephalopathy (HE), which is a brain dysfunction resulting from liver insufficiency or porto-systemic shunting [3]. HE is caused by accumulation in the bloodstream of toxins that are normally removed by the liver and it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subtle neuropsychological alterations to coma [3]. The clinical diagnosis of HE is based on the Conn score, which ranges from 0 to 4, with higher scores indicating more severe mental and psychomotor impairment. According to the severity of the manifestation, HE can be classified as covert HE (CHE, Conn score 0-1) – described as subtle neuro-psychological abnormalities such as alterations in attention, psychomotor speed, working memory and visuospatial ability – or overt HE (OHE, Conn score 2-4) – ranging from clinically visible signs of confusion, space and time disorientation, personality change to coma [3,4]. Covert HE occurs in about 60% and OHE in about 30-40% of patients with cirrhosis at some point during their clinical course, and patients with a previous episode of OHE have a 1-year cumulative risk of recurrence of 40% [5-7]. HE may adversely affect lives of patients, with cumulative deficits in cognitive function and diminished health related quality of life (HRQoL) across both physical and mental domains[8,9]. The 1-year and 5-year mortality associated with HE are higher (64% and 85%) than those associated with other major complications of cirrhosis, such as variceal bleed (20% and 63%) and ascites (29% and 58%) [10]. The severity of this complication is emphasised by the strong association between history of OHE and mortality. In a study of patients with liver cirrhosis and a history of recurrent OHE episodes, survival rates were 42% at one year and 23% at three years following an OHE episode [11]. The occurrence of a HE episode of Conn score 2 in patients with cirrhosis was associated with a 4-fold increase in mortality [12].

The number of patients with HE in England and Wales remains uncertain since there is not a specific code for HE within the current international classification of diseases (ICD-10) schedule [13]. It is estimated that in England and Wales 60,000 people have cirrhosis, and of these, based on a crude calculation, about (60%) 36,000 may have CHE, of whom about (60%) 21,000 may develop an OHE episode within three years of CHE diagnosis [5,14,15]. Whilst patients in remission, or experiencing CHE symptoms, may be managed effectively in the community, patients experiencing an OHE episode are usually admitted to hospital for treatment. Recurrent HE episodes are a distressing aspect of chronic liver disease for both patients and their carers; they consume considerable NHS resources [16] and are associated with poorer prognosis [17]. Reduction in recurrence of episodes of OHE is therefore an important treatment goal for patients with liver cirrhosis.

Key recommendations for the secondary prevention of OHE come from the joint EASL/AASLD guideline published in 2014, where rifaximin-α is recommended as add-on to lactulose therapy [1,3]. Rifaximin-α, a poorly absorbable, broad spectrum, oral antibiotic, is thought to inhibit the division of urea-deaminating bacteria, thereby reducing the intestinal production of ammonia and other compounds that are believed to be important to the pathogenesis of HE [18]. Following an

OHE event, rifaximin-α can be used for reducing the recurrence of OHE episodes in patients ≥18 years.

In the pivotal randomised controlled trial (RCT) of rifaximin-α (RFHE001), patients with chronic liver disease and in remission from at least two OHE episodes (Conn score 0 or 1) were randomly allocated to receive rifaximin-α 550 mg twice daily or placebo for 6 months; 91% of patients in both groups received concomitant lactulose [19]. Rifaximin-α was found to significantly reduce the risk of an OHE episode and HE-related hospitalisations compared with placebo, with significant improvements also demonstrated in HRQoL [9,19]. An open-label maintenance (OLM) study (RFHE002, extension of the RCT) conducted over 24 months to examine the longer term impact of rifaximin-α, demonstrated a continued reduction in the rate of HE-related and all-cause hospitalisations with rifaximin-α use, together with a well-tolerated safety profile [20].

In March 2015, the National Institute for Health and Care Excellence (NICE) published guidance, Technology Appraisal 337 (TA 337), recommending rifaximin-α use within its marketing authorization [21]. The original submission in 2013 was centred on both the clinical effectiveness and cost-effectiveness of rifaximin-α assessed on findings from the pivotal RCT [19]. Subsequent to the original submission, real world data from four individual UK audits became available [22-25] and were included as an addendum in the NICE submission of 2014.

The purpose of this analysis is to provide a clearer determination of the value for money of rifaximin-α for treating people with HE using trial data and real world evidence used in the NICE TA 337.

Methods

Evaluation approach

A cost-effectiveness analysis of the use of rifaximin-α plus optional concomitant lactulose versus placebo plus optional concomitant lactulose was undertaken using a Markov state transition model. The specified model structure captured clinical outcomes that would be observed in current practice: time to first breakthrough OHE episode, aligned with the pivotal RCT's primary outcome [19], and subsequent breakthrough of HE episodes following periods of remission. A cohort of 1,000 patients was entered into both arms of the model. This cohort consisted of adult cirrhotic patients in remission (Conn score 0-1) from recurrent OHE episodes (at least two prior episodes), reflecting the patient characteristics of those enrolled in the pivotal RCT [19]. The treatment arms in the model were also aligned to this same study, where patients received rifaximin-α 550 mg twice daily with or without lactulose or placebo with or without lactulose; in the pivotal RCT, 91% of patients in both arms were taking concomitant lactulose [19].

The analysis was undertaken from the perspective of the UK National Health Service. The base-case time horizon was five years, which reflects the typical life expectancy of patients with cirrhosis and a history of OHE [10,11]. The cycle length was one month, in line with the interval at which data were collected during the pivotal RCT, and was considered sufficiently short to avoid over-estimating outcomes and resource use, thus no half-cycle correction was applied. Health effects were measured in quality adjusted life years (QALYs), using the Chronic Liver Disease Questionnaire (CLDQ) mapped to EuroQol five dimensions questionnaire (EQ-5D). The discount rate was 3.5% for both benefits and costs as recommended by the Treasury [26]. Prices are in 2012 prices (UK £). The values for key variables used in the model are detailed in Table 1.

Model structure and key features

The costs and benefits of the introduction of rifaximin-α were estimated using a state transition approach that reflected the clinical pathway of patients with liver disease and recurrent OHE, where OHE episodes alternate with remission periods (Figure 1). The model comprised five health states:

(1) CHE 1 (CHE-1) – The model starting state. Patients in this state were in remission from a previous OHE event (Conn score 0 or 1)
(2) OHE 1 (OHE-1) – The first breakthrough episode of OHE (Conn grade 2, 3 or 4) following model start. Whilst in OHE 1 patients were at risk of hospitalisation
(3) CHE 2 (CHE-2) – Remission state post OHE 1 and all subsequent OHE events
(4) OHE 2 (OHE-2) – Captured all subsequent episodes of OHE following model start. Whilst in OHE-2 patients were at risk of hospitalisation
(5) Death – Captured death of patients from CHE-1, OHE-1, CHE-2 and OHE-2 states

Patients entered the model in a covert state, CHE-1, and transitioned to the overt state OHE-1 when experiencing a breakthrough episode of OHE. Following a breakthrough episode, patients in OHE-1 would enter into a subsequent remission state, CHE-2, and would remain there pending subsequent episodes of HE during which they would transition to OHE-2. Following resolution of the OHE episode, patients would transition from OHE-2 back to CHE-2 where they would be at risk of further OHE events captured as transitions into OHE-2. From each of these states (CHE-1, OHE-1, CHE-2, OHE-2) patients could exit the model in case of death.

Key model transition probabilities

Transition probabilities applied in the analysis were derived from the RCT [19], from unpublished individual patient level data from the follow-up OLM study [20], and from a post-hoc analysis of the OLM trial [20] (Table 1); patient characteristics of the OLM study have been published [20]. Time to first breakthrough OHE episode for the rifaximin-α and placebo arms were extracted from a Kaplan-Meier (KM) analysis from the pivotal RCT for the period 0 to 168 days [19]. Unpublished patient level data for rifaximin-α patients who did not experience a breakthrough OHE event during the RCT phase [19] and were enrolled in the OLM study [20] were used to derive a KM curve for first breakthrough OHE event from 168 to 1008 days. These two datasets were combined and parametric survival distributions were fitted. Akaike information criterion (AIC), Bayesian information criterion (BIC) and visual inspections were also consulted to determine best model fit, resulting in selection of a lognormal distribution. The model assumed full recovery after 30.4 days following a breakthrough OHE episode, where patients re-entered a subsequent covert state (CHE-2) after one cycle; this assumption was applied for all OHE events. Patients in the remission state following an OHE event (CHE-2) were at risk of further OHE events. To estimate the transition between CHE-2 and OHE-2, unpublished patient level data were used to estimate the time to the first subsequent OHE event (i.e. the second event following entry into the RCT or OLM). The same methods (described above) used to derive the transition probabilities for time to first breakthrough event were applied to derive subsequent OHE events. The process found that the lognormal distribution provided the best fit for time to subsequent OHE events. The risk of an OHE episode was found to be greater in CHE-2 than when patients entered the model in CHE-1. Patients in the CHE-2

state were at risk of having further OHE episodes and, in the current model, the transition probability applied for all other subsequent OHE events was assumed to be the same as that applied for the first subsequent OHE event. This is likely to be a conservative assumption as risk of further OHE events increases with the number of prior OHE events [17].

Mortality

The model inputs for mortality in the four health states (CHE-1, CHE-2, OHE-1 and OHE-2) were the same for the rifaximin-α and lactulose cohorts.

Patients were at risk of both HE-related mortality and all-cause mortality in all model cycles. Data from a post-hoc analysis of the OLM study were sourced to characterise disease-related mortality [17]. The baseline mortality in the model was the additive combination of the HE-related and all-cause mortality.

The mean age of the patient population under consideration in the pivotal study was 56 years, and this was adopted in the base-case analysis [19]. 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 converted to monthly probability of death by age from Interim Life Tables for England and Wales by the Office of National Statistics [27]. Mortality risk was adjusted to incorporate the weighted average of the ratio of males to females in the original RCT [19]. Disease related mortality inputs were obtained by using the best-fit parametric proportional hazards survival models from the OLM [20]. In the CHE-1 state the best fit was found to be a log normal distribution and in the CHE-2 state a Weibull distribution [17]. The probability of mortality was higher in the CHE 2 state compared to CHE1 state. The 30-day mortality risk associated with the first breakthrough episode of HE (OHE-1) and subsequent OHE episode (OHE-2) were 11.0% (standard error (SE) 0.03) and 7.7% (SE 0.02), respectively. These mortality rates were calculated from the OLM study [20], and adjusted to include all-cause mortality.

Hospitalisation and length of stay

Results from a meta-analysis using data from four individual UK centres [22-25] investigating the impact of treatment with rifaximin-α on hospital resources in UK clinical practice were used for hospitalisations and length of stay in the model [21,28]. These interim data were subsequently validated in a more comprehensive study of a larger number of UK centres [16]. Two endpoints were analysed, hospitalisations and total bed days. A constant event rate was assumed in annualising the data presented by each study, which had varying observation periods. Mean difference in each primary endpoint was tested with a continuous random-effects model using the DerSimonian-Laird method to allow for heterogeneity between studies. A mean difference of 22.2 (95% CI; 9.1-35.3; $p<0.001$) annual bed days per patient before and after rifaximin-α was observed. A mean difference of 1.3 (0.7-1.8; $p<0.001$) annual hospitalizations per patient before and after rifaximin-α was observed. The reduction of 44% in hospitalizations and 66% reduction in bed days were implemented in the model [28].

Health-related utility

Health-related utility was estimated indirectly from disease-specific quality of life data (CLDQ) collected from the pivotal study [29]. These data showed that during the covert/remission state there were significant improvements in the health-related QoL (HRQoL) of patients in the rifaximin-α plus lactulose group compared with patients taking placebo plus lactulose [9]. The relationship between the disease-specific (CLDQ) [30] and generic HRQoL(EQ-5D) data can be seen in Figure 2[29]. In the lactulose group, patients in CHE-1 and CHE-2 had a utility value of 0.588. Patients treated with rifaximin-α had an incremental change in EQ-5D of 0.106 relative to the lactulose group. This utility increment was applied in the model for both the CHE-1 and CHE-2 states for rifaximin-α treated patients. In both model arms, patients in OHE-1 and OHE-2 had a utility value of 0.538 The utility values applied in the model were adjusted to incorporate the effect of ageing. The average age of the modelled cohort was extracted from the pivotal RCT [19]. UK population norms were extracted from Kind and colleagues (Table 1) [31].

Financial costs

The drug acquisition costs used in the model were based on published costs from the British National Formulary for lactulose and for rifaximin-α [32]. The dosage of rifaximin-α was one 550 mg tablet twice daily. The unit price of a 56-tablet pack of rifaximin-α was £259.23 (Table 1). The recommended starting dose for lactulose is 30 to 50 mL three times daily, and subsequently adjusted to produce two to three soft stools daily. The dose was taken from the published RCT [19]. The mean dose of concomitant lactulose was 3.14 cups per day for patients on rifaximin-α and 3.51 cups per day for patients on placebo (1 cup is 10 g lactulose/15 mL). Given that the price of lactulose was £2.28 per 500 mL, the cost of concomitant lactulose is calculated as £6.54 per month for patients on rifaximin-α and £7.31 per month for patients on placebo. Patients were assumed to receive medication over the entirety of the modelled time horizon.

Expert opinion, sought to determine the frequency of outpatient visits for patients in remission, suggested that patients were reviewed every 3-6 months in an outpatient setting. Based on NHS Reference Costs, the unit cost for an outpatient visit was £176.27, and with a frequency of outpatient visits assumed to be every three months (base-case analysis), the total cost applied in the model for the remission health state was £58.75 per month [33].

In the OHE state, the model assumed that all patients incurred the cost of an additional outpatient visit (£176.27) [33]. Furthermore, those patients who had a hospitalisation incurred additional costs. To estimate the cost per day in the OHE state, a weighted average of all non-elective inpatient (long stay) HRG procedure codes beginning with GC from NHS Reference Costs was used [33]. These reference costs were applied to the duration of stay calculated in the meta-analysis described above. The total cost for a patient in the overt health state was £10,180 and £6,779 for rifaximin-α and placebo, respectively (Table 1).

Sensitivity and scenario analysis

Deterministic and probabilistic sensitivity analysis was undertaken on all variables using the values

and distributions outlined in Table 1. A scenario analysis was run applying health state utility values derived from SF-36 trial data mapped to SF-6D utility values.

Results

Likelihood of being in a key clinical state

At three years, of the 1000 patients that entered the model, 42.7% of patients assigned to the placebo plus lactulose arm were in the CHE2 state; this was 6.9% higher than the corresponding number in the rifaximin-α plus lactulose arm. At the same time point, 60.4% of rifaximin-α-treated patients had experienced a breakthrough OHE event compared to 79.4% of the placebo-treated patients. Of the patients that entered the model, 34.0% and 41.7% had died at three years in the rifaximin-α and placebo arms respectively.

Differences in mortality arose from the reduced numbers of OHE episodes in the rifaximin-α group by two mechanisms, avoidance of the acute 30-day mortality associated with OHE-1 and OHE-2[8], and longer retention in the CHE-1 state with exposure to a lower hazard of death than equivalent cases who transition to the CHE-2 state having recovered from OHE-1.

Incremental cost-effectiveness ratio values for the base case scenario (5 years), and at alternative time horizons

The average cost for the included elements of care at five years was £22,971 in the rifaximin-α arm and £23,545 in the lactulose arm, a cost saving of £573. The corresponding values for benefit were 2.35 QALYs and 1.83 QALYs per person, respectively, a difference of 0.52 QALYs. This translated into a dominant base-case scenario (i.e. lower costs and improved health outcomes). The ICER at two years was also dominant. Whilst only a small number of subjects will survive more than five years because they are so severely ill, it was possible to generate a theoretical ICER value at 10 years (£4,470 per QALY gained, 3.43 years on rifaximin), and running the model to a lifetime horizon (£7,215 per QALY gained, 4.42 years on rifaximin-α) (Table 2).

Sensitivity analysis

Deterministic sensitivity analysis illustrates that the model was insensitive to most parameters (Figure 3). Varying the real-world data by using the 95% confidence interval around the mean difference in bed days per person per year resulted in a mean ICER of -£17,014 (dominant) per QALY gained and £17,168 per QALY gained. Since rifaximin-α has been shown to reduce both the frequency of hospital admission and the length of hospital stay, variation in this factor has a notable impact on the base case ICER [16]. Following this, the parametric distribution of rate of progression to OHE was found to exert influence on model results.

A probabilistic sensitivity analysis is illustrated in the cost effectiveness plane (Figure 4). Here not all results are dominant but the likelihood of rifaximin-α being cost effective at the conventional level of £30,000 per QALY gained was >99%.

When SF-6D utility data were applied in the model a higher number of QALYs were generated in the rifaximin-α and lactulose arm of the model (2.563 QALYs) compared with the rifaximin-α and lactulose arm (1.753 QALYs). Total costs in each arm were unchanged and consequently rifaximin-α plus lactulose was dominant when compared to placebo plus lactulose.

Discussion

Patients in the morbid phase of end stage liver failure are severely ill, with low life expectancy, unless in receipt of a successful liver transplant. HE, one of the major complications of advanced liver disease, is both difficult to manage and financially costly. The present health economic evaluation shows that the use of rifaximin-α to reduce the recurrence of OHE episodes improves clinical outcomes and is cost saving. In economic parlance, rifaximin-α in combination with lactulose is dominant over standard care with lactulose alone.

The economic model presented was based on the six month rifaximin-α registration study, unpublished analyses of patient level data from the OLM study conducted over 24 months, and the post-hoc analysis of the OLM [17,19,20]. Health-related utility was estimated indirectly from disease-specific quality of life data from the pivotal study [9], while resource use data describing the impact of rifaximin-α on hospital admissions and length of stay within the NHS were from single-centre UK audits [22-25]. From the clinical data analysed, it was clear that repeated OHE episodes can adversely affect patients' quality of life and yield significant burden on healthcare resources. The present health economic analysis demonstrated that add-on rifaximin-α to lactulose for management of patients with history of OHE is a cost-effective option, because, by reducing the number of OHE episodes as well as hospital admissions and stay, rifaximin-α improves patients quality of life and reduces the overall costs associated with the care of these patients. In particular, the average cost per patient for the included elements of care was £22,971 in the rifaximin-α plus lactulose arm and £23,545 in the lactulose alone arm, with a saving of £573. The corresponding values for benefit were 2.35 QALYs and 1.83 QALYs per patient, respectively, with a difference of 0.52 QALYs. This translated into a dominant base-case ICER over the 5-year horizon. Furthermore, in our analysis the cost-effectiveness of rifaximin-α was found to be robust following a range of methods of examining the sensitivity of the resulting ICER to factors that were known to be uncertain.

From the analysis of patient level data, it was clear that repeated OHE episodes can have a significant impact on the mortality of patients, since being in the overt state increases your chance of death. By modelling this effect, our analysis estimated the importance of using rifaximin-α to reduce recurrent OHE episodes in patients with history of OHE.

As in all economic evaluations of this nature, this model was the result of the distillation of a range of data from various sources. As highlighted by deterministic sensitivity analysis (Figure 3) our summary value of dominance is heavily influenced by the results from a meta-analysis [28] of four individual UK audits [22-25] that estimated a 44% reduction in annualised bed days per patient treated with rifaximin-α compared to standard of care. This finding was supported by recently published real world data from a retrospective, multicentre study of 7 UK hospitals, that found a reduction in hospital length of stay ranging from 31% (annualised data) to 53% (3-month data) following initiation of rifaximin-α. This resulted in an annual cost saving between £1,480 and £3,228 per patient when taking into account drug costs for 1-year rifaximin-α treatment [16].

Clinical benefits of rifaximin-α over-and-above an evident reduction in the risk of OHE events have been postulated [17]. Questions now remain about how early these benefits could be achieved by managing patients earlier in the natural history of their liver disease.

Conclusion

Rifaximin-α 550 mg twice daily in patients with recurrent HE in the context of liver cirrhosis not only produced clinical benefits resulting in improved health related utility, but also represented good value for money compared to standard care by reducing episodes of OHE and associated hospital resource use.

Table 1. Key parameters included in the evaluation.

Variable	Value	Lower CI	Upper CI	Distribution	Source
Dosage					
Average daily dose of lactulose - placebo arm	52.65	52.25	53.05	Normal	RFHE3001 (19)
Average daily dose of lactulose - rifaximin arm	47.10	46.75	47.45	Normal	RFHE3001
Costs					
Rifaximin tablet price	£4.63	4.63	4.63	None	BNF 63
Lactulose price (500 mL)	£2.28	2.28	2.28	None	BNF 63
Cost of outpatient visit	£110.68	£110.51	£110.84	Gamma	NHS ref. cost(33)
Liver Failure Disorders with Interventions	£3,483.86	£3,235.97	£3,731.75	Gamma	NHS ref. cost(33)
Liver Failure Disorders without Interventions	£2,028.42	£1,922.02	£2,134.83	Gamma	NHS ref. cost(33)
Non-Malignant Liver Disorders with Catastrophic CCs	£3,988.26	£3,700.39	£4,276.14	Gamma	NHS ref. cost(33)
Non-Malignant Liver Disorders with Severe CCs	£3,084.07	£2,882.30	£3,285.83	Gamma	NHS ref. cost(33)
Non-Malignant Liver Disorders with Major CCs	£2,421.08	£2,320.36	£2,521.80	Gamma	NHS ref. cost(33)
Non-Malignant Liver Disorders without Major CCs	£1,795.26	£1,715.41	£1,875.12	Gamma	NHS ref. cost(33)
Hospitalisations					
Percentage hospitalised - placebo arm	100%	100%	100%	None	UK RWD (28)
Percentage hospitalised - rifaximin arm	100%	100%	100%	None	UK RWD (28)
Length of stay - days (placebo)	30.6	30.6	30.6	None	UK RWD (28)
Percentage reduction in LOS (rifaximin)	34%	-40.5%	99%	None	UK RWD (28)
1st episode					
Lognormal regression treatment parameter	1.10	0.57	1.62	None	RFHE3001 PLD
Lognormal regression constant parameter	1.80	1.45	2.14	None	RFHE3001 PLD
Lognormal regression /ln_sig parameter	0.62	0.47	0.77	None	RFHE3001 PLD
Subsequent episode					
Lognormal regression treatment parameter	-1.09	-1.62	-0.56	None	RFHE3002 PLD

Variable	Value	Lower CI	Upper CI	Distribution	Source
Lognormal regression constant parameter	1.38	0.99	1.77	None	RFHE3002 PLD
Lognormal regression /ln_sig parameter	0.55	0.37	0.74	None	RFHE3002 PLD
Health-related utility					
Duration of HE episode disutility – days	11	1	28	Normal	KOL ad-board
EQ-5D population norm (all population)	0.86	0.85226	0.86774	Normal	
EQ-5D population norm (population aged <25)	0.94	0.92651	0.95349	Normal	
EQ-5D population norm (population aged 25-34)	0.93	0.91929	0.94071	Normal	
EQ-5D population norm (population aged 35-44)	0.91	0.89676	0.92324	Normal	UK Population Norms for EQ-5D (31)
EQ-5D population norm (population aged 45-54)	0.85	0.81440	0.88560	Normal	
EQ-5D population norm (population aged 55-64)	0.80	0.77684	0.82316	Normal	
EQ-5D population norm (population aged 65-74)	0.78	0.75693	0.80307	Normal	
EQ-5D population norm (population aged 75+)	0.73	0.70014	0.75986	Normal	
CLDQ-EQ5D conversion factor	0.143	0.131	0.154	Normal	RFHE3001 PLD(29)
CLDQ rifaximin-increment	0.743	0.182	1.303	Normal	Sanyal 2011(9)
SF-36 baseline utility	0.568	0.539	0.597	Beta	RFHE3001 PLD
SF-36 baseline-adjusted rifaximin-utility increment	0.190	0.179	0.200	Normal	RFHE3001 PLD
Mortality					
Lognormal regression constant parameter (covert)	5.36	4.38	6.35	None	RFHE3002 PLD
Lognormal regression /ln_sig parameter (covert)	0.65	0.33	0.97	None	RFHE3002 PLD
30-day prob (overt)	0.11	0.06	0.16	Beta	RFHE3002 (20)
Weibull regression constant parameter (sub-covert)	-3.62	-4.36	-2.88	None	RFHE3002 PLD
Weibull regression /ln_sig parameter (sub-covert)	0.80	0.56	1.14	None	RFHE3002 PLD
30-day prob (sub-overt)	0.08	0.04	0.11	Beta	RFHE3002 (20)

MVN: multi-variate normal

Table 2. Incremental cost effectiveness ratio (ICER) at varying time horizons.

	Lactulose		Rifaximin				
Time horizon	QALY	Cost	QALY	Cost	Δ QALY	Δ Costs	ICER
2 years	0.97	£16,852	1.20	£13,170	0.23	-£3,681	-£15,916
5 years	1.83	£23,545	2.35	£22,971	0.53	-£573	-£1087
10 years	2.58	£27,330	3.43	£31,153	0.86	£3,823	£4,470
Lifetime	3.19	£29,552	4.42	£38,432	1.23	£8,880	£7,215

References

[1] National Institute for Health and Care Excellence. Cirrhosis in over 16s: assessment and management. 2016.

[2] M.K. Nadim, F Durand, J.A. Kellum, J. Levitsky, J.G. O'Leary, C.J. Karvellas, et al, Management of the critically ill patient with cirrhosis: A multidisciplinary perspective, J Hepatol. 64 (2016) 717–35.

[3] H. Vilstrup, P. Amodio, J. Bajaj, J. Cordoba, P. Ferenci, K.D. Mullen, et al, Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases, J Hepatol. 61 (2017) 642–59.

[4] J.S. Bajaj, J. Cordoba, K.D. Mullen, P. Amodio, D.L. Shawcross, R.F. Butterworth, et al, Review article: the design of clinical trials in hepatic encephalopathy--an International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) consensus statement, Aliment Pharmacol Ther. 33 (2011) 739–47.

[5] A. Das, R.K. Dhiman, V.A. Saraswat, M. Verma, S.R. Naik. Prevalence and natural history of subclinical hepatic encephalopathy in cirrhosis. J Gastroenterol Hepatol. 16 (2001) 531–5.

[6] P. Amodio, F. Del Piccolo, E. Pettenò, D. Mapelli, P. Angeli, R. Iemmolo, et al, Prevalence and prognostic value of quantified electroencephalogram (EEG) alterations in cirrhotic patients, J Hepatol. 35(2001) 37–45.

[7] B.C. Sharma, P. Sharma, A. Agrawal, S.K. Sarin, Secondary prophylaxis of hepatic encephalopathy: an open-label randomized controlled trial of lactulose versus placebo, Gastroenterology. 137 (2009) 885–91, 891.e1.

[8] J.S. Bajaj, C.M. Schubert, D.M. Heuman, J.B. Wade, D.P. Gibson, A. Topaz, et al, Persistence of cognitive impairment after resolution of overt hepatic encephalopathy, Gastroenterology. 138 (2010) 2332–40.

[9] A. Sanyal, Z.M. Younossi, N.M. Bass, K.D. Mullen, F. Poordad, R.S. Brown, et al, Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy – a double-blind placebo-controlled study, Aliment Pharmacol Ther. 34 (2011) 853–61.

[10] P. Jepsen, P. Ott, P.K. Andersen, H.T. Sorensen, H. Vilstrup, Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. Hepatology. 51 (2010) 1675–82.

[11] J. Bustamante, A. Rimola, P.J. Ventura, M. Navasa, I. Cirera, V. Reggiardo, et al, Prognostic significance of hepatic encephalopathy in patients with cirrhosis, J Hepatol. 30 (1999) 890–5.

[12] C.A. Stewart, M. Malinchoc, W.R. Kim, P.S. Kamath, Hepatic encephalopathy as a predictor of survival in patients with end-stage liver disease, Liver Transpl. 13 (2007) 1366–71.

[13] World Health Organisation. ICD-10: international statistical classification of diseases and related health problems: tenth revision. — 2nd ed. 2004.

[14] NHS Atlas of Variation in Healthcare for People with Liver Disease. 2013.

[15] K.R. Patidar, L.R. Thacker, J.B. Wade, R.K. Sterling, A.J. Sanyal, M.S. Siddiqui, et al, Covert hepatic encephalopathy is independently associated with poor survival and increased risk of hospitalization, Am J Gastroenterol. 109 (2014) 1757–63.

[16] J.G. Orr, C.J. Currie, E. Berni, A. Goel, K.J. Moriarty, A. Sinha, et al, The impact on hospital resource utilisation of treatment of hepatic encephalopathy with rifaximin-alpha, Liver In. 36 (2016) 1295–303.

[17] C.A. Bannister, J.G. Orr, A.V. Reynolds, M. Hudson, P. Conway, A. Radwan, et al, Natural History of Patients Taking Rifaximin-alpha for Recurrent Hepatic Encephalopathy and Risk of Future Overt Episodes and Mortality: A Post-hoc Analysis of Clinical Trials Data, Clin Ther. 38 (2016) 1081–1089.e4.

[18] G. Bongaerts, R. Severijnen, H. Timmerman, Effect of antibiotics, prebiotics and probiotics in treatment for hepatic encephalopathy, Med Hypotheses. 64 (2005) 64–8.

[19] N.M. Bass, K.D. Mullen, A. Sanyal, F. Poordad, G. Neff, C.B. Leevy, et al, Rifaximin Treatment in Hepatic Encephalopathy, N Engl J Med. 362 (2010) 1071–81.

[20] K.D. Mullen, A.J. Sanyal, N.M. Bass, F.F. Poordad, M.Y. Sheikh, R.T. Frederick, et al, Rifaximin is safe and well tolerated for long-term maintenance of remission from overt hepatic encephalopathy, Clin Gastroenterol Hepatol. 12 (2014) 1390–7.e2.

[21] National Institute for Health and Care Excellence, Rifaximin for preventing episodes of overt hepatic encephalopathy, 2015.

[22] A. Goel, N. Patel, R. Blackwell, S. Crompton, K. Moriarty. Rifaximin treatment in Hepatic Encephalopathy: Marked reduction in hospital admissions and hospital bed day occupancy in a District General Hospital in the UK, BSG. 2014.

[23] T. Valliani, M. Sumner, F. Gordon, Rifaximin Treatment in Hepatic Encephalopathy – a single centre experience, Falk Found. 2012.

[24] J. Orr, F. Perez, H. Mitchison, M. Hewett, S. Saksena, J. Topping, et al, Rifaximin for Hepatic Encephalopathy is Cost Effective at Reducing Emergency Hospital Admission, BSG. 2013.

[25] J. Roach, T. Heron, E. Henry, J.F. Dillon. The Real World Experience of Rifaximin in Hepatic Encephalopathy, Falk Found. 2013.

[26] H M Treasury, The Green Book: Appraisal and Evaluation in Central Government, 2013.

[27] Office for National Statistics. Interim Life Tables: England and Wales, 2010-2012. [Internet]. [cited 2014 Jun 13]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/interimlifetables/previousReleases

[28] Norgine Pharmaceuticals Limited (Data on file), Meta-analysis of the impact of treatment with rifaximin-α on hospital resources in UK clinical practice DOF-XIFAX-006. 2015.

[29] E. Berni, C. Bannister, C.D. Poole, P. Conway, K. Nanuwa, C.J. Currie, PWE-154 The First Evaluation Of The Relationship Between The Chronic Liver Disease Questionnaire And The Eq-5d Index In Hepatic Encephalopathy Patients Treated With Rifaximin-a, Gut, 63 (2014) A192 LP-A192.

[30] Z.M. Younossi, G. Guyatt, M. Kiwi, N. Boparai, D. King. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease, Gut, 45 (1999) 295–300.

[31] P. Kind, G. Hardman, S. Macran. UK Population Norms for EQ-5D, Cent Heal Econ. 1999;

[32] Joint Formulary Committee. British National Formulary (online) [Internet]. BMJ Group and Pharmaceutical Press. [cited 2017 Jun 29]. Available from: http://www.medicinescomplete.com

[33] Department of Health. NHS Reference costs. 2011;