The clinical and cost-effectiveness of rifaximin for maintaining remission from episodes of hepatic encephalopathy

A critique of the submission from Norgine

Addendum to the report submitted on 26th April 2013

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Title

The clinical and cost-effectiveness of rifaximin for maintaining remission from episodes of hepatic encephalopathy. Addendum to the report submitted on 26th April 2013.

Source of funding

This report was commissioned by the NIHR HTA Programme as project number 11/38/01

Produced by

Matrix
Peninsula Technology Assessment Group (PenTAG)

Although Matrix are primarily responsible for the work in this report, PenTAG retains responsibility for the standard of the report and the quality of the advice that it contains.

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Acknowledgements

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Declaration of competing interest of the authors

None

Rider of responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows

Bacelar M, Bertranou E, Cooper C, Hyde C, Venkatachalam, M. The clinical and cost-effectiveness of rifaximin for maintaining remission from episodes of hepatic encephalopathy. Addendum to the report submitted on 26th April 2013, Matrix and Peninsula Technology Assessment Group, 2013.

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Date completed

May 2013

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1.0 Introduction

Norgine's submission considered the use of rifaximin-α (Targaxan®) for the reduction in the recurrence of episodes of overt hepatic encephalopathy (HE) in patients 18 years of age and older. In the study used for the submission, 91.3% of the patients were using concomitant lactulose. The comparator used was placebo with concomitant lactulose.

This report presents additional analysis undertaken by the ERG. Section 2 is organised as follows:

- Section 2.1 considers the impact on the final ICER of the trial data chosen to populate the model, the distribution used to extrapolate time to first HE episode, and the timeframe of the analysis.
- Section 2.2 refers to the impact on the final ICER of changes in mortality rates.
- Section 2.3 provides details on the impact of hospitalisation rates and costs on the results of the model.
- Section 2.4 describes health related quality of life (HRQoL) data different from that chosen by Norgine for their model.

2.0 Additional analysis undertaken by the ERG

2.1 Trial data, distributions, and timeframes

NICE requested that additional results were presented to illustrate the impact on the final ICER of three factors:

- The trial data chosen to populate the model
- The distribution used to model time to first HE episode
- The timeframe of the analysis

Tables 1 and 2 present the final ICERs for the 5-year and the 10-year analyses, respectively. In both tables, the first column presents the results when data extrapolated from both trials RFHE3001 and RFHE3002 is used, and the second column presents the results when data extrapolated only from trial RFHE3001 is used. For the sake of completeness, the third column presents the results for non-extrapolated (hence distribution invariant) data from both trials.

The final ICER in the base case scenario selected by Norgine (£22,298 - indicated in bold in Table 1) takes a 5-year timeframe, is based on data extrapolated from both trials, and relies on the lognormal distribution.

Table 1. Impact on final ICERs of using different distributions, 5-year analysis

5-year analysis	Extrapolation from combined RFHE3001 and RFHE3002	Extrapolation from RFHE3001	RFHE3001 & RFHE3002[1]
Exponential	£14,438	£20,230	£21,424
Weibull	£27,825	£20,102	£21,424
Gompertz	£13,740	£27,139	£21,424
Lognormal	**£22,298**[2]	£29,038[3]	£21,424
Loglogistic	£21,006	£23,164	£21,424

[1] Even though these data were not extrapolated, some assumptions were made in the economic model to generate transition probabilities beyond the 6 months data trial (RFHE3001) and the 2 years data trial (RFHE3002).

[2] This ICER corresponds to the base case value with the corrections made by the ERG (Bacelar et al, 2013 p.73).

[3] We identified a potential mistake in one of the parameters of the Lognormal regression from RFHE3001 suggesting that this ICERs might not be reliable. We were not able to correct this as the value was hardcoded.

Table 2. Impact on final ICERs of using different distributions, 10-year analysis

10-year analysis	Extrapolation from combined RFHE3001 and RFHE3002	Extrapolation from RFHE3001	RFHE3001 & RFHE3002[1]
Exponential	£11,380	£15,652	£15,680
Weibull	£19,143	£15,065	£15,680
Gompertz	£10,482	£21,144	£15,680
Lognormal	£16,546	£21,137[3]	£15,680
Loglogistic	£15,705	£17,212	£15,680

[1] Even though these data were not extrapolated, some assumptions were made in the economic model to generate transition probabilities beyond the 6 months data trial (RFHE3001) and the 2 years data trial (RFHE3002).
[2] This ICER corresponds to the base case value with the corrections made by the ERG (Bacelar et al, 2013 p.73).
[3] We identified a potential mistake in one of the parameters of the Lognormal regression from RFHE3001 suggesting that this ICERs might not be reliable. We were not able to correct this as the value was hardcoded.

The results in Tables 1 and 2 show that:

- **Timeframe**: as expected the 10-year analysis generates lower ICERs than the 5-year analysis
- **Extrapolated data**: with the exception of the Weibull distribution, using data from both trials tends to generate lower ICERs than using data only from RFHE3001.
- **Distribution**: for the 5-year analysis and when data from both trials is used, the ICERs range from £13,000 to £28,000. This £15,000-difference between ICERs tends to decrease when data only from RFHE3001 is used, and when the timeframe of the analysis is extended to 10 years.

Figure 1 shows the survival curves for different distributions using data from both trials and Figure 2 shows the curves when data only from RFHE3001 is used.

Figure 1. Survival curves for different distributions using the combined dataset (RFHE3001 and RFHE3002) extrapolated over 5 years

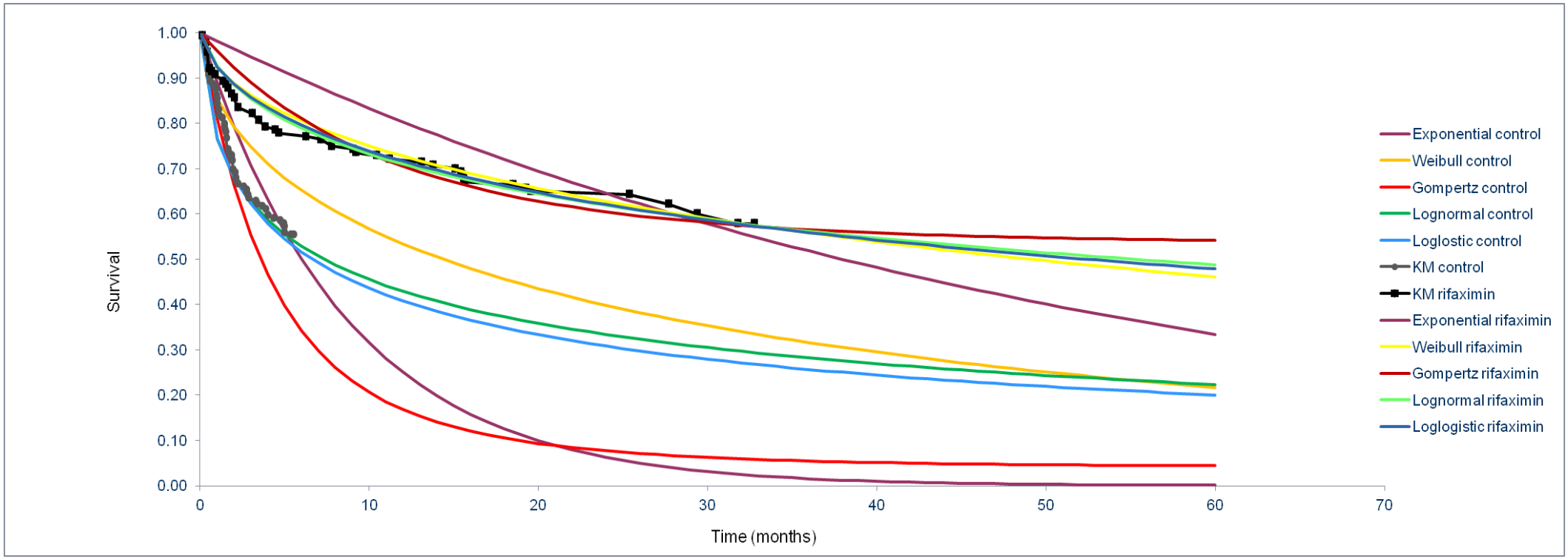
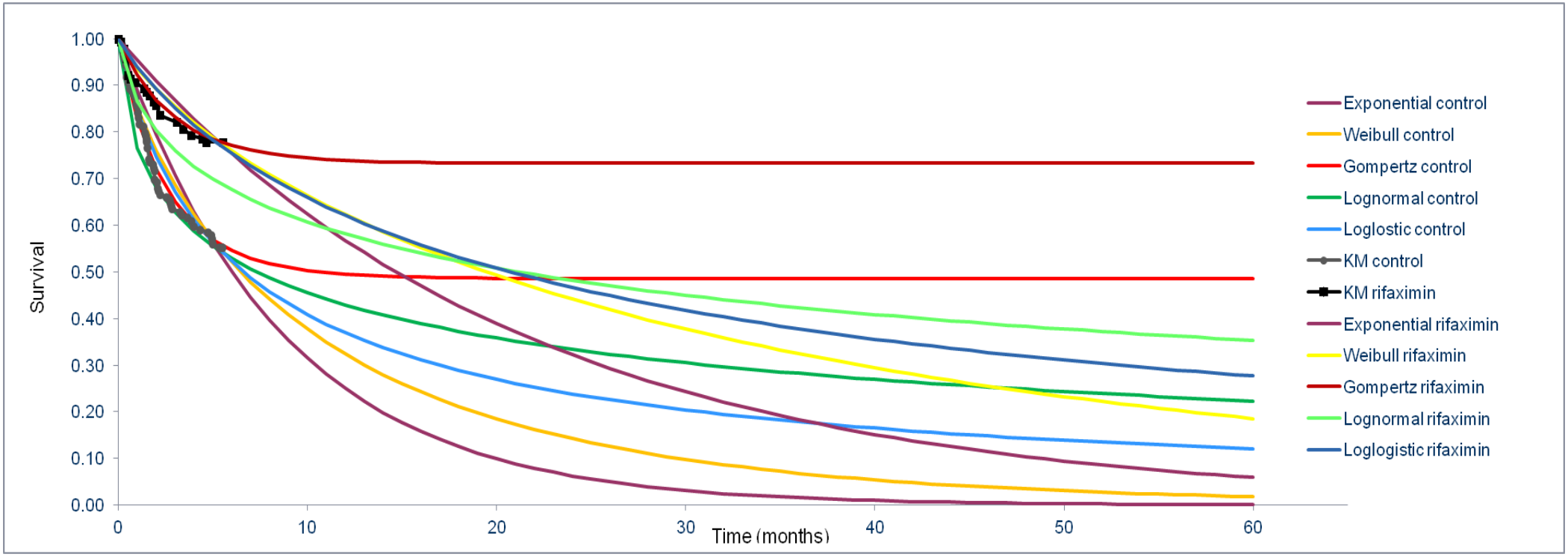


Figure 2. Survival curves for different distributions using the RFHE3001 data alone extrapolated over 5 years



It is worth noticing in Figure 1 that the gradient of the Kaplan-Meier curve tends to be steeper in the first six months of the trial, whilst after month 6th the occurrence of HE episodes seems to occur at a slower pace. As a result of this concentration of HE episodes in the first six months (corresponding to the RFHE3001 timeframe):

- The survival curves estimated using data from both trials potentially overestimate the effect of rifaximin in the first six months.
- The survival curves estimated using data only from RFHE3001, potentially underestimate the effect of rifaximin after the first six months.

Based **purely on visual inspection** (as the ERG does not have enough data to carry out other validation methods), when data from both trials is used, the lognormal distribution provides the best fit to the data (as indicated in Norgine's submission). When data only from RFHE3001 is used, the Gompertz distribution seems to provide the best fit. Therefore, solely on the basis of visual inspection, and considering the potential overestimations and underestimations pointed above, the 5-year ICER is likely to range between £22,298 and £27,139.

2.2 Mortality data

As stated in the ERG report, although Norgine considered that the mortality data from trial RFHE3001 was not mature enough to capture the drug overall impact on survival, the model submitted captures the effect on mortality of rifaximin vs. placebo through the reduction in the recurrence of HE events. The reduced mortality rate associated with such reduction is a major source of QALYs gained.

To estimate the mortality associated with the overt state (i.e. HE event), an overall weighted mortality risk was obtained by taking the proportion of patients within each Conn score category and attaching a mortality estimate to it. Conn score specific mortality rates were obtained through expert opinion and Shawcross et al (2011). Based on the expert opinion sought by the ERG, the mortality assumed for the Conn score categories 3 and 4 might be an overestimate. If the mortality associated with these states was changed to reflect lower values, the overall mortality rate in the overt state would decrease, which would drive the final ICER upwards.

Tables 3 and 4 explores the impact of changing the mortality rates for the Conn score categories 3 and 4 on the final ICER over a 5 year and a 10 year time horizon. In the first row we present the base case scenario while in the second and third row we present the scenarios considering a reduction of mortality of 5 and 10 percentage points, respectively. As expected, when reducing the overall mortality associated with the overt state, the final ICERs tend to increase.

Table 3. Impact on final ICERs of reducing overall mortality, 5-year analysis

5-year analysis	Extrapolation from combined RFHE3001 and RFHE3002 using the lognormal distribution
Base case Conn score mortality: Grade 3 – 54% Grade 4 – 72%	**£22,298**[1]
5% point reduction Conn score mortality: Grade 3 – 49% Grade 4 – 67%	£23,285
10% point reduction Conn score mortality: Grade 3 – 44% Grade 4 – 62%	£24,412

[1] This ICER corresponds to the base case value with the corrections made by the ERG (Bacelar et al, 2013 p.73).

Table 4. Impact on final ICERs of reducing overall mortality, 10-year analysis

10-year analysis	Extrapolation from combined RFHE3001 and RFHE3002 using the lognormal distribution
Base Case Conn score mortality: Grade 3 – 54% Grade 4 – 72%	£16,546
5% point reduction Conn score mortality: Grade 3 – 49% Grade 4 – 67%	£17,062
10% point reduction Conn score mortality: Grade 3 – 44% Grade 4 – 62%	£17,648

2.3 Hospitalisation costs

Hospitalisation rates and costs were not considered a key driver of the final ICER. NICE requested further analysis of hospitalisation rates and costs to better understand this result. In response to this:

- Figure 3 presents the percentage of patients experiencing an HE episode. As expected, given that rifaximin was proved to be effective in reducing the recurrence of HE episodes, the percentage of patients experiencing an HE episode is higher in the placebo arm than in the rifaximin arm.
- Figure 4 presents the percentage of hospitalised patients among those who experienced an HE episode. This shows a higher hospitalization rate in the rifaximin arm (14.63%) compared with the placebo arm (10.71%). Norgine estimated these rates based on data from trial RFHE3001.
- Figure 5 illustrates total hospitalisation costs (for a cohort of 1,000 patients). This shows higher total costs in the placebo arm than in the rifaximin arm. However, the difference tends to decrease over time, and by month 60th there is virtually no difference between the two arms.

Therefore, the reasons why hospitalisation costs do not represent a main driver for the ICER can be summarised as follows:

- More patients experience an HE episode in the placebo arm than in the rifaximin arm.
- However, among those who experienced an HE episode, the hospitalisation rate is higher in the rifaximin arm.

These two factors act as opposite forces in the sense that the first one brings the ICER downwards, whilst the second one drives the ICER upwards. Hence, the overall effect of hospitalisation costs on the final ICER is to some extent neutralised.

Figure 3. Percentage of patients experiencing an HE episode

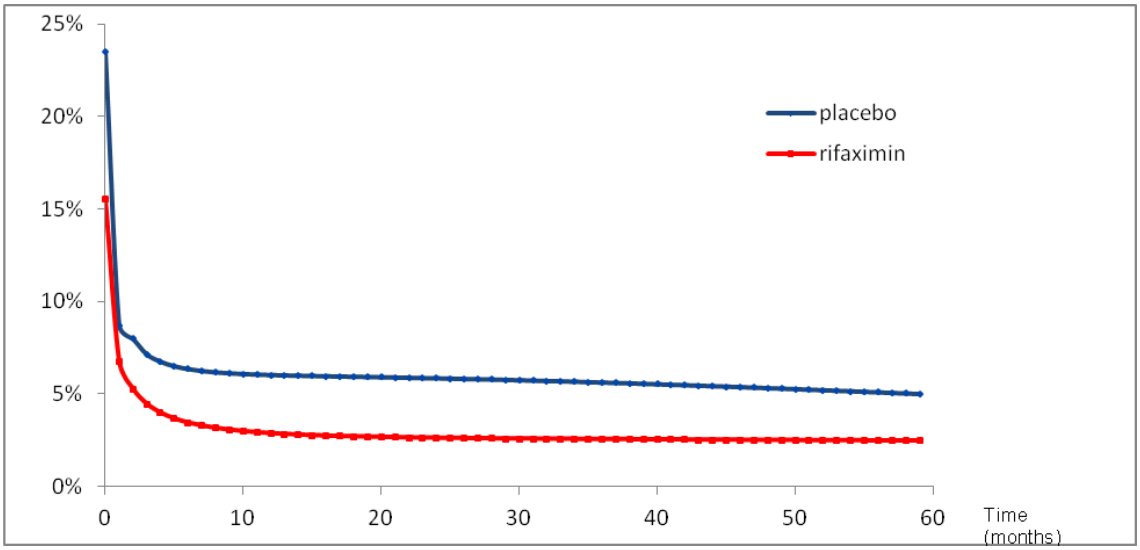


Figure 4. Percentage of patients hospitalised given that they had experienced an HE episode

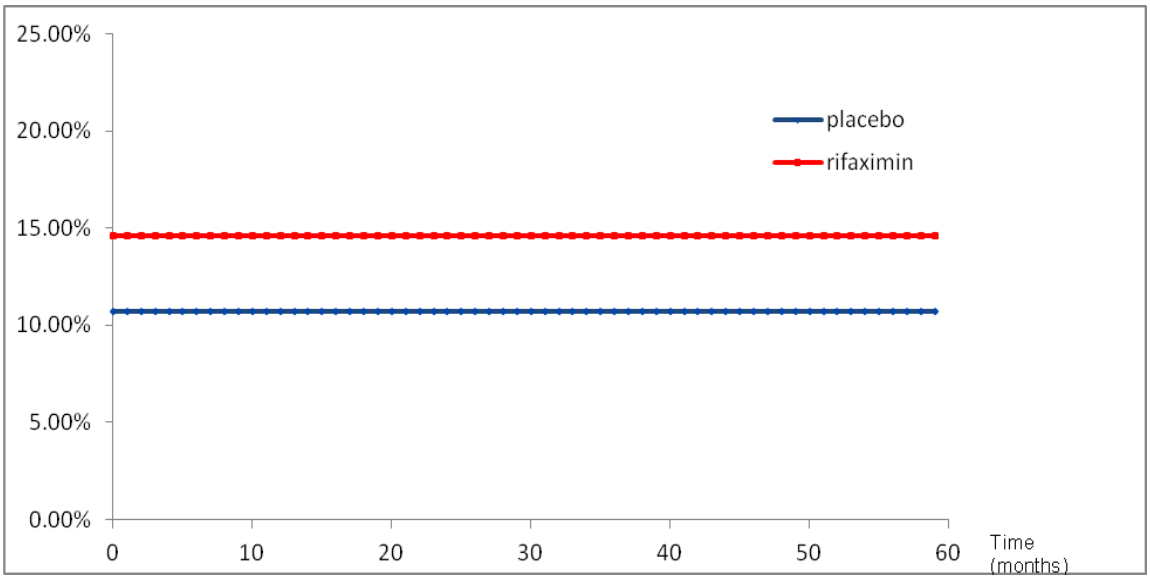
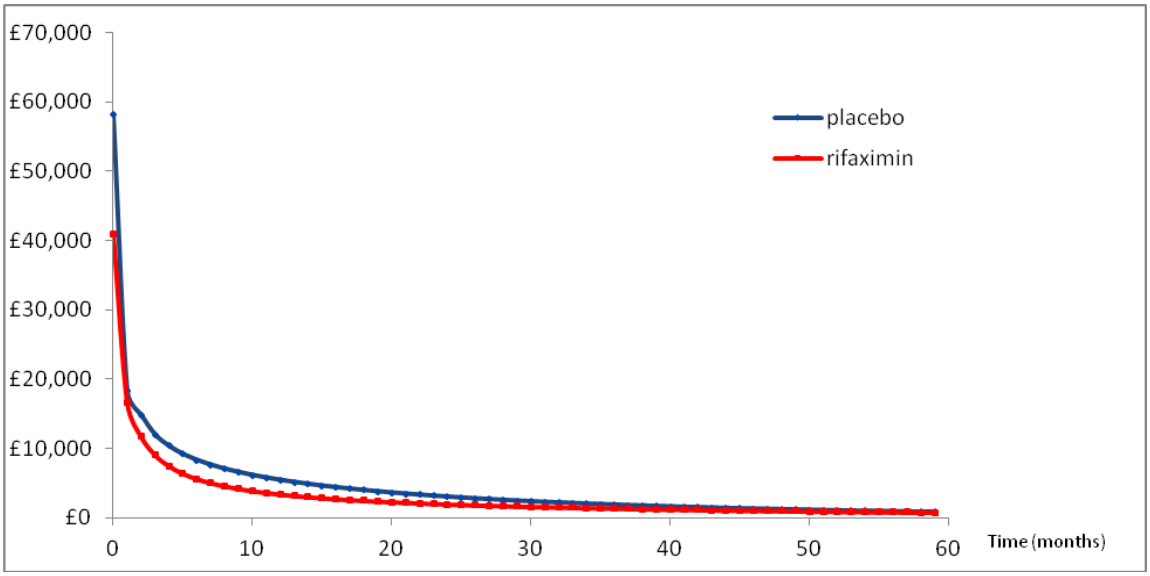


Figure 5. Total hospitalisation costs



2.4 Health Related Quality of Life (HRQoL)

It was mentioned on the ERG report that the utilities used in Norgine's economic model were elicited as CSM for the general population in a study commissioned by Norgine.

While the preferred measure of HRQoL in adults according to NICE is the EQ-5D, it was requested that the ERG looked into a study measuring the quality of life for HE patients utilizing the Chronic Liver Disease Questionnaire (CLDQ).

The ERG appreciated this reference and analysed the study.
The aim of Sanyal et al, 2011 study was to evaluate the effect of rifaximin on health-related quality of life (HRQL) in cirrhotic patients with HE, by looking into the CLDQ domains (for example fatigue and abdominal symptoms) and the change in these from baseline and after 6 months of using rifaximin.

Patients with cirrhosis in remission from HE (Conn score category of 0 or 1) and a documented history of recurrent HE episodes were randomised to rifaximin 550 mg twice daily or placebo for 6 months. Concomitant lactulose was permitted during the study. The CLDQ was administered every 4 weeks. A longitudinal analysis using time-weighted averages of the CLDQ scores normalised by days on study therapy was used to evaluate the effect of treatment on HRQL.

The results showed that treatment with rifaximin had a consistent favourable impact on the HRLQ as measured by CLDQ scores for patients with cirrhosis and HE.
The time-weighted averages of the overall CLDQ score and each domain score were significantly higher in the rifaximin group vs. placebo (p-values ranged from 0.0087 to 0.0436); and were significantly lower in patients who experienced a HE breakthrough compared to those who remained in remission (p-values were <0.0001).

The analysis undertaken by Sanyal et al, 2011 is not likely to have an impact on the manufacturer submission since:

- The same approach was already undertaken by the manufacturer. During RFHE3001 trial, patients ranked their level of fatigue on the CLQD scale and this was included as a study outcome in the manufacturer's submission.
- The final scores produced by the CLQD are not directly comparable to the standard utility scale (considering the 0 to 1 utility scale).

Furthermore, the manufacturer collected utility data using the SF-36. It was Norgine assessment that given the completion of SF-36 at discrete time points and the short duration and infrequent occurrence of HE episodes, it was unlikely that the detriment in quality of life resulting from HE episodes had been properly captured.

The final approach of eliciting utility values from the general population seems a reasonable one.

3.0 References

Bacelar M, Bertranou E, Cooper C, Hyde C, Venkatachalam, M. The clinical and cost-effectiveness of rifaximin for maintaining remission from episodes of hepatic encephalopathy. Single Technology Appraisal NIHR HTA Programme (11/38/01), Matrix and Peninsula Technology Assessment Group, 2013.

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