Rifaximin STA - Norgine Response to ERG Clarification Questions

Section A: Statement of the decision problem (Section 5 of STA submission)

A1. **Priority Question:** The base case analysis in the submission is based on a comparison of rifaximin with placebo (with both treatment groups receiving concomitant lactulose as per the clinical trial). However, the comparators defined by NICE in the final scope are lactulose, neomycin and neomycin with lactulose.

- Please provide further justification why you have chosen to compare rifaximin with placebo (with concomitant lactulose in both arms) in the base case rather than the listed comparators.

Response

As outlined in Norgine's response to the draft scope in this appraisal, lactulose is considered to be the current standard of care and is routinely used in clinical practice. As per the SmPC and the pivotal study by Bass et al, 2010 ~91% of the patients on rifaximin and placebo were using concomitant lactulose.

Whilst there are no therapies required for co-administration of rifaximin, according to the licensed indication, the evidence presented in the submission is largely from the use of rifaximin plus concomitant lactulose versus lactulose alone. In clinical practice rifaximin will be administered concomitantly with lactulose in the majority of cases in order to reduce further episodes of hepatic encephalopathy (HE).

In the submission, Norgine have compared rifaximin (plus concomitant lactulose) with the most appropriate comparator, lactulose alone (termed 'placebo' throughout the submission). The comparison in the base case is based on the ITT population in the pivotal study (Bass et al, 2010) in which ~91% of patients received concomitant lactulose in the rifaximin and placebo arms. This is considered appropriate for use in the base case analysis as it avoids breaking the pivotal trial randomisation and reflects clinical practice.

Post-hoc analyses for the population in the pivotal study that received concomitant lactulose (~91% of the ITT population) and those that did not (~9% of the ITT population) were not pre-planned or formally undertaken. However, as suggested by NICE prior to submission we provided data for both of the subgroups in the clinical and economic sections of the submission.

Neomycin is not licensed for the reduction in recurrence of episodes of overt HE. Neomycin is also not commonly used in clinical practice for long-term prevention of HE recurrence. The neomycin SPC contains warnings against long-term use. Norgine has previously highlighted this in the response to the draft scope of this appraisal where it was stated that there is no clinical data to support the use of neomycin in the prevention of recurrence of hepatic encephalopathy in patients in remission. No controlled trials with neomycin have demonstrated equal or superior

efficacy to lactulose. In addition, the long term use of neomycin is also associated with the risk of ototoxicity and nephrotoxicitity.

Furthermore, 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. In summary, we consider that the overall neomycin usage is minimal and as the data source does not specify an indication we believe that this usage is likely to be across a number of different indications.

No trials were identified that allowed a comparison between rifaximin and neomycin and rifaximin and neomycin/lactulose as outlined in our submission (see Section 6.1 and 6.2). Therefore there is no evidence for the efficacy of neomycin or neomycin and lactulose in combination in this indication to inform the submission in the population outlined in the decision problem.

- The ERG has identified a 6 month trial of rifaximin compared with neomycin which could be relevant to the appraisal (Miglio F et al Rifaximin, a non-absorbable rifamycin, for the treatment of hepatic encephalopathy. Current medical research and opinion 1997;13(10):539-601. Please reconsider including neomycin as a comparator or alternatively, present any justification for excluding it in the light of this study.

Response

Norgine also identified Miglio et al, 1997 in the clinical systematic review of the literature that was undertaken. However, the study was subsequently excluded for the following reasons:

- Patient population
    - The patient population was chronic HE rather than patients with HE who had been in remission and therefore did not match the patient population in the decision problem.
    - Patients in the study had a Conn score of 1 or 2. This meant that some patients were not in remission when recruited into the trial and therefore did not match the patient population in the decision problem.
    - No detail on prior episodes reported. This was stated as an exclusion criterion in the systematic review so that the patient population in any identified studies would be similar enough to include in a meta-analysis or indirect comparison.
- Treatments
    - Both treatments (rifaximin and neomycin) were given for 14 consecutive days of every month. This did not represent the licensed dose for rifaximin nor how rifaximin would be used in

clinical practice. Consequently, a comparison between the two studies (Bass et al, 2010 and Miglio et al, 1997) would have been inappropriate.

- Outcomes
  - Miglio et al, 1997 did not report either of the following outcomes:
    - time to first breakthrough episode of hepatic encephalopathy or time to first hospitalisation involving hepatic encephalopathy (the primary and secondary endpoints in Bass et al 2010, respectively).
  - The clinical and safety assessments in Miglio et al, 1997 were outlined as follows:
    - "The treatment was considered effective when an improvement of at least one grade of HE was detected. Adverse events and their relationship to treatment were monitored during all of the study period."
  - The results reported were as follows:
    - In all patients a clear-cut progressive reduction in HE grade, with no difference between the two treatment groups, was observed. In particular, the improvement in HE was already statistically significant after 30 days ($p<0.001$ for each group).
    - No further information on grade of HE over time was reported.
  - The differences in outcomes between Miglio et al, 1997 and Bass et al, 2010 meant that inclusion of this study in comparing rifaximin with neomycin was completely inappropriate with respect to statistical analysis.

Consequently, due to differences in the patient population, treatment regimens and outcomes stated above, it was considered inappropriate to use this study to inform a comparison of neomycin with rifaximin.

Section B: Clarification on effectiveness data (Section 6 of STA submission)

B1. For trial RFHE3001, to complete the information on randomisation and blinding, please provide a description of the placebo and indicate if it was tested that the intervention was indistinguishable from the placebo.

Response

The following information regarding the identity of the Investigational Product is taken from the clinical study report, (Reference: Norgine Data on File. RFHE3001. CSR Page 37-38)

The study drug was supplied by Salix. Rifaximin tablets were supplied as pink-coloured, coated, oval, biconvex tablets. Placebo was supplied as tablets that were identical to the rifaximin tablets (excluding active moiety).

Rifaximin 550 mg and matching placebo tablets were provided in matching bottles.

Manufacturers and lot numbers for rifaximin tablets and matched placebo tablets are presented in table 1.

The study complied with all applicable laws and regulatory requirements.

Table 1: Investigational Product

Study Drug	Manufacturer	Formulation	Lot Numbers
Rifaximin	Patheon Whitby Operations 111 Consumer Drive Whitby, ON L1N 5Z5 CANADA	550 mg tablet	C5H0192, C5J0043, and C6L00261
Placebo	Patheon Whitby Operations 111 Consumer Drive Whitby, ON L1N 5Z5 CANADA	Matching 550 mg tablet	C5H0243, C5I0387, and C6K01131

B2. In trial RFHE3001, please explain the difference in the numbers in the intervention (140) and control (159) arms given the 1:1 randomisation schedule.

Response

(Reference: Norgine Data on File. RFHE3001. CSR page 58)

A total of 299 subjects were randomised to receive placebo (159 subjects) or rifaximin (140 subjects) in this study between December 2005 and August 2008. The United States and Canada analysis region included 219 subjects and 80 subjects were randomised and treated in Russia.

The randomisation code for this study included a block size of 4 and was stratified by site.

Because the number of subjects at each site was not a multiple of 4, there was some imbalance between treatment groups (159 subjects in the placebo group and 140 subjects in the rifaximin group).

B3. **Priority Question**: For trial RFHE3002, please provide the Kaplan-Meier curves to first episode between those “new to rifaximin” and “continuing rifaximin” separately, instead of together as provided in the submission.

Response

[redacted]

B4. In trial RFHE3001, patients were excluded once the first episode of hepatic encephalopathy had occurred. However, the submission states that some of these patients were eligible to join trial RFHE3002. Therefore could you please provide:

- The number of people who joined trial RFHE3002 under “continuing rifaximin” who were excluded from trial RFHE3001 due to experiencing a first episode. That is, how many of the 70 patients in the second trial (RFHE3002) had experienced an episode of hepatic encephalopathy with rifaximin within the first trial (RFHE3001).

Response

[redacted]

- **Priority Question:** For these patients, at what point did their first episode occur in the first trial (RFHE3001) and if there was an episode for these patients in the second trial (RFHE3002) at what point did this occur?

Response:

[redacted]

B5. For trial RFH3002, it is stated that patients can continue on treatment even if an episode of hepatic encephalopathy occurs. Can you please provide data on:

- The number of individuals who continued on treatment despite an episode of hepatic encephalopathy.

Response

[redacted]

- **Priority Question:** For these patients, at what time point did the first episode occur and at what time did any subsequent episodes occur?

Response

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Section C: Clarification on cost-effectiveness data (Section 7 of STA submission)

C1. Please explain why the identified economic study Huang et al (2007), on page 92 of the submission, was not considered to be relevant and consequently excluded.

Response

As stated in section 7.1.2 of the main submission, the population in Huang et al, 2007 did not reflect the 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. A summary of the study was provided for completeness.

C2. Page 97 of the submission currently states that a five-year time horizon adequately captures the health benefits and costs relevant to this appraisal. Please provide additional justification for this and also explain any other reasoning for why a 5 year time horizon for the economic analyses was considered appropriate.

Response

A 5 year time horizon was deemed to be appropriate in capturing the costs and benefits of rifaximin treatment, based on expert opinion, data from the open label extension study RFHE3002 and a number of publications summarised below.

[redacted]

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 (please see reference 12 in the main submission).

In a retrospective medical chart review investigating the clinical course of alcohol-related cirrhosis in a cohort of 466 Danish patients, Jepsen et al. 2010 (19) reported

that the 5 year survival probability for patients with hepatic encephalopathy was 15% (please see reference 19 in the main submission).

Given the varying mortality stated above, in conjunction with advice from hepatologists, a 5 year time horizon was selected.

C3. **Priority Question:** As stated on page 98, the recommended dose for lactulose is 30 – 50ml 3 times daily (90ml-150ml per day). However, in the RFHE3001 study the mean dose of lactulose taken by patients was 3.14 – 3.51 cups per day which is equivalent to 47ml – 53ml per day based on the conversion metric provided. Please explain why the dose of lactulose taken by patients in the trial is less than the recommend dose.

Response

(Reference: Norgine Data on File. RFHE3001. CSR Page 39-40)

It is important to highlight that RHE3001 was a study of rifaximin versus placebo, not rifaximin versus lactulose.

Lactulose use was optional for subjects during the study if subjects were already receiving lactulose at baseline. Lactulose was available to subjects throughout the study.

If the subject was receiving lactulose at baseline, then dose modifications (i.e. reductions, increases, stopping and restarting lactulose therapy) were permitted as needed throughout the study.

To summarise, any lactulose use was optional and in line with the clinical needs of the patient, both prior to and during the study.

C4. **Priority Question:** It is noted that a Lognormal distribution was used to fit the combined dataset (RFHE3001 and RFHE3002) and to extrapolate the study results beyond six months.

- Please justify the choice of the Lognormal distribution.

Response

The choice of the lognormal distribution was based on results of the AIC and BIC statistics and visual inspection of fitted curves. The analysis has been re-run on the combined dataset (RFHE3001 and RFHE3002) for rifaximin patients with the inclusion of the Gamma distribution and the corresponding AIC and BIC statistics are provided below.

Of the tested distributions the lognormal curve generated the lowest AIC and BIC statistic and visual inspection suggested a good fit to the data. The Gamma distribution was not included in the original tested distributions because the parameterisation cannot be readily employed in an economic model in MS Excel. The method used to generate transition probabilities for the scenario analysis in response to the ERG queries used a built-in function within STATA and is inaccessible. It is not possible to model parameter uncertainty in the predicted transition probabilities. Testing with the Gamma distribution suggested little difference between this and the lognormal distribution. The lognormal distribution is the more parsimonious model and therefore represents a reasonable choice for the base case time to event distribution.

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	394.8565	400.7097
Gompertz	140	.	-200.2804	2	404.5609	410.4442
Gamma	140	.	-192.4214	3	390.8428	399.6678

- More specifically, please provide Log-cumulative hazard plots to assess the underlying accelerated failure time assumption in the Lognormal distribution.

Response

[redacted]

[redacted]

- It is understood that the combined trial data were fitted to the Exponential, Weibull, Gompertz, Lognormal and Logistic distributions. For sake of completeness, please provide a scenario where the Gamma distribution is used to fit the data and the respective coefficients or provide the rationale for excluding its use. We also ask that you justify the choice of the distributions tested in the sensitivity analysis (page 133).

Response

Due to differences in parameterisations between STATA and Excel the predict survival command in STATA was employed to generated expected survival probabilities (cumulative probability of not experiencing an overt HE episode) at discrete time points (months 1 to 60) for the Gamma distribution.

The base case analysis presented in the submission had separate curves fitted to the combined dataset (RFHE3001 and RFHE3002) for rifaximin patients and the 6 month data (RFHE3001) for the lactulose patients. The shape parameter in the regression on the 6 month data was replaced with the shape parameter from the regression on the combined dataset to extrapolate beyond the 6 month (RFHE3001) trial results for lactulose patients.

The STATA predict survival command was used separately on the combined dataset for rifaximin patients and the 6 month data for lactulose patients (the common shape

parameter approach is not replicated in this analysis). The regression output for both regressions, the estimated survival probabilities and corresponding transition probabilities, and the estimated ICER are presented below.

Gamma regression – accelerated failure-time form

[Fitted to the combined dataset (RFHE3001 and RFHE3002) for rifaximin patients]

_t	Coef.	Std. Err	z	P>|z|	[95% Conf.	Interval]
_cons	2.444222	1.159993	2.11	0.035	.1706768	4.717767
/ln_sig	1.145083	.1161507	9.86	0.000	.9174314	1.372734
/kappa	-1.507674	.9675038	-1.56	0.119	-3.403946	.3885987
sigma	3.142701	.365027			2.502853	3.946124

[Fitted to 6 month data (RFHE3001) for lactulose patients]

_t	Coef.	Std. Err	z	P>|z|	[95% Conf.	Interval]
_cons	.5357108	.4668529	1.15	0.251	-.379304	1.450726
/ln_sig	.5755994	.1246746	4.62	0.000	.3312416	.8199572
/kappa	-1.998064	.6878703	-2.90	0.004	-3.346266	-.6498634
sigma	1.778196	.2216959			1.392696	2.270403

Transition probabilities - Rifaximin

Month	S(t)	S(t-u)	1-S(t)/S(t-u)
1	0.922777	1	7.72%
2	0.869151	0.922777	5.81%
3	0.832169	0.869151	4.25%
4	0.804054	0.832169	3.38%
5	0.781433	0.804054	2.81%
6	0.762548	0.781433	2.42%
7	0.746367	0.762548	2.12%
8	0.732233	0.746367	1.89%
9	0.719702	0.732233	1.71%
10	0.708458	0.719702	1.56%
11	0.698272	0.708458	1.44%
12	0.688968	0.698272	1.33%
13	0.680412	0.688968	1.24%
14	0.672497	0.680412	1.16%
15	0.665139	0.672497	1.09%
16	0.658267	0.665139	1.03%
17	0.651824	0.658267	0.98%
18	0.645762	0.651824	0.93%
19	0.640041	0.645762	0.89%
20	0.634627	0.640041	0.85%

21	0.629489	0.634627	0.81%
22	0.624603	0.629489	0.78%
23	0.619946	0.624603	0.75%
24	0.615498	0.619946	0.72%
25	0.611244	0.615498	0.69%
26	0.607166	0.611244	0.67%
27	0.603253	0.607166	0.64%
28	0.599493	0.603253	0.62%
29	0.595873	0.599493	0.60%
30	0.592386	0.595873	0.59%
31	0.589021	0.592386	0.57%
32	0.585772	0.589021	0.55%
33	0.582631	0.585772	0.54%
34	0.579591	0.582631	0.52%
35	0.576647	0.579591	0.51%
36	0.573793	0.576647	0.49%
37	0.571024	0.573793	0.48%
38	0.568336	0.571024	0.47%
39	0.565723	0.568336	0.46%
40	0.563183	0.565723	0.45%
41	0.560711	0.563183	0.44%
42	0.558305	0.560711	0.43%
43	0.555961	0.558305	0.42%
44	0.553675	0.555961	0.41%
45	0.551447	0.553675	0.40%
46	0.549272	0.551447	0.39%
47	0.547149	0.549272	0.39%
48	0.545075	0.547149	0.38%
49	0.543048	0.545075	0.37%
50	0.541066	0.543048	0.36%
51	0.539128	0.541066	0.36%
52	0.537231	0.539128	0.35%
53	0.535375	0.537231	0.35%
54	0.533557	0.535375	0.34%
55	0.531776	0.533557	0.33%
56	0.53003	0.531776	0.33%
57	0.528319	0.53003	0.32%
58	0.526641	0.528319	0.32%
59	0.524995	0.526641	0.31%
60	0.523379	0.524995	0.31%

Transition probabilities - Lactulose

Month	S(t)	S(t-u)	1-S(t)/S(t-u)
1	0.83346	1	16.65%
2	0.716626	0.83346	14.02%
3	0.64866	0.716626	9.48%
4	0.602452	0.64866	7.12%
5	0.568132	0.602452	5.70%
6	0.54118	0.568132	4.74%
7	0.519192	0.54118	4.06%
8	0.500746	0.519192	3.55%
9	0.484942	0.500746	3.16%
10	0.471175	0.484942	2.84%
11	0.459021	0.471175	2.58%
12	0.448172	0.459021	2.36%
13	0.438398	0.448172	2.18%
14	0.429523	0.438398	2.02%
15	0.42141	0.429523	1.89%
16	0.41395	0.42141	1.77%
17	0.407055	0.41395	1.67%
18	0.400652	0.407055	1.57%
19	0.394684	0.400652	1.49%
20	0.3891	0.394684	1.41%
21	0.383857	0.3891	1.35%
22	0.378921	0.383857	1.29%
23	0.374262	0.378921	1.23%
24	0.369852	0.374262	1.18%
25	0.365669	0.369852	1.13%
26	0.361693	0.365669	1.09%
27	0.357906	0.361693	1.05%
28	0.354293	0.357906	1.01%
29	0.35084	0.354293	0.97%
30	0.347535	0.35084	0.94%
31	0.344368	0.347535	0.91%
32	0.341327	0.344368	0.88%
33	0.338405	0.341327	0.86%
34	0.335594	0.338405	0.83%
35	0.332885	0.335594	0.81%
36	0.330273	0.332885	0.78%
37	0.327753	0.330273	0.76%
38	0.325317	0.327753	0.74%
39	0.322961	0.325317	0.72%
40	0.320682	0.322961	0.71%
41	0.318473	0.320682	0.69%
42	0.316332	0.318473	0.67%

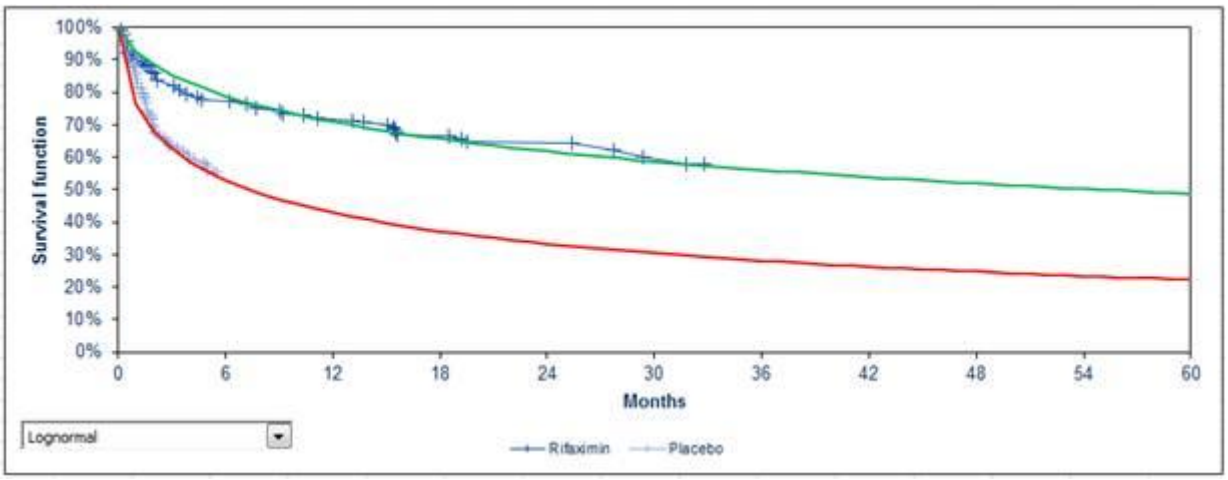
43	0.314256	0.316332	0.66%
44	0.312239	0.314256	0.64%
45	0.310281	0.312239	0.63%
46	0.308377	0.310281	0.61%
47	0.306525	0.308377	0.60%
48	0.304722	0.306525	0.59%
49	0.302967	0.304722	0.58%
50	0.301257	0.302967	0.56%
51	0.29959	0.301257	0.55%
52	0.297965	0.29959	0.54%
53	0.296378	0.297965	0.53%
54	0.294829	0.296378	0.52%
55	0.293317	0.294829	0.51%
56	0.291839	0.293317	0.50%
57	0.290394	0.291839	0.49%
58	0.288982	0.290394	0.49%
59	0.2876	0.288982	0.48%
60	0.286248	0.2876	0.47%

Results – Gamma distribution

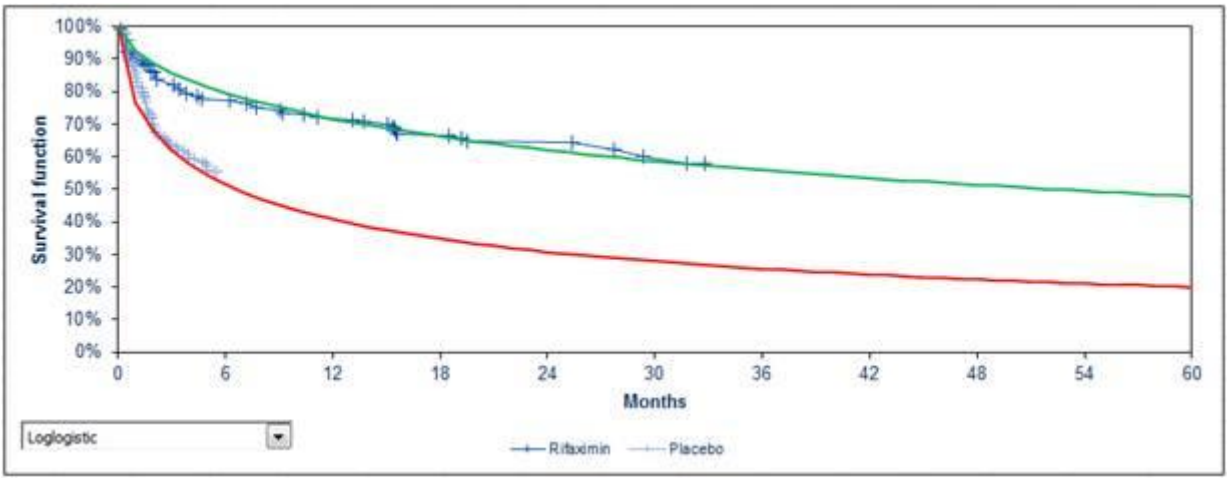
Treatment	Total costs	Total QALYs	ICER
Rifaximin	£5,164.34	1.2163	£25,752.13
Lactulose	£814.21	1.0474	
difference	*£4,350.14*	*0.1689*	

Exponential, Weibull and Gompertz distributions were tested to show the results using distributions based on the proportional hazards metric. The log logistic distribution was tested and the graphs were visually inspected. It was decided not to present them in the main body of the submission as the results were similar to those for the log normal distribution. The distribution can be readily tested by changing the distribution choice on the first worksheet of the model. The difference in plots and cost effectiveness results are presented below:

Lognormal curves:



Log logistic curves:



<u>Results – log logistic distribution</u>

Treatment	Costs	QALYs	ICER
Rifaximin	£5,168.21	1.2179	£23,185.87
Lactulose	£820.71	1.0304	
difference	*£4,347.50*	*0.1875*	

C5. **Priority Question:** For Table 38 (page 117), could you please explain:

- Why Conn score 1 is considered to be an overt episode and included in the weighted QALY estimate?

Response

An episode of HE in the clinical trial was defined as "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", therefore a Conn score of 1 was also included in determining utility values for overt episodes for completeness.

- Why the percentage of patients with a hepatic encephalopathy episode does not add to 100%?

Response

This is due to missing data in the clinical trial. The patient level data reported the number of patients with a Conn score of 1-4 when an overt episode was experienced. 7 patients did not have a documented Conn score. However, these patients were included in the denominator when the percentage of patients with each Conn score related to HE episode was calculated.
By excluding the 7 patients whose Conn score was not available from the clinical trial and re-weighting the percentages to add up to 100%, the model base case ICER is reduced from £23,186 to £21,929. Therefore, we consider the approach taken to be conservative.

C6. **Priority Question:** Could you please confirm and clarify the calculations in Table 39 (page 117). Values reported as daily seem to be monthly, and we have not been able to replicate your calculations.

Response

Thank you for bringing this to our attention. We have updated the table below.

[redacted]

C7. **Priority Question:** The base-case results (table 50, page 128) have not been presented in the required format. Please refer to the STA submission template (table B24, page 53) for the preferred format of presenting the base-case results which should include the incremental results. Please present the results accordingly.

Response

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Placebo	820.71	1.0304	-	-	
Rifaximin	5168.21	1.2179	4347.50	0.1875	£23,186
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

Section D: Textual clarifications and additional points (Appendices)

D1. **Priority Question:** Appendix 2: Effectiveness search

- Please clarify why the Medline/Cochrane search was not updated for the submission.
- Please clarify why the Embase and Econlit searches were only run to 2010.

Response

An updated search was conducted on 12th and 13th Dec 2012. Please see **Appendix A** for details of the search strategy. The search only identified a number of 'kin' abstracts that provide no additional information above and beyond that which has already been described in the submission.

D2. **Priority Question:** Appendix 8: Adverse effects

- Please clarify why separate searches for adverse events literature were not undertaken outside of the methodologically limited effectiveness and cost-effectiveness searches.

Response

A separate search for adverse events was not deemed necessary as these searches are rarely completed separately. Furthermore, with data on adverse effects being reported in the clinical trials these were identified in the clinical systematic review.

D3. **Priority Question:** Appendix 10: Cost-effectiveness search

- Please clarify why the search was not updated for the submission

Response:

An updated systematic literature review was conducted to identify relevant cost-effectiveness and resource use studies pertaining to rifaximin-α, as well to lactulose, neomycin, and neomycin + lactulose per the decision problem. Please see **Appendix B** for details of the search strategy.

The search identified two potentially relevant economic evaluations (Bajaj et al and Paul et al) since 2010.

On full review Bajaj et al (2012) was not considered to be relevant as the study assesses the cost effectiveness of diagnosis as well as treatment and the outcome was reduction in motor vehicle accidents and therefore does not address the current decision problem.

Paul et al (2012) was considered to be relevant but not enough data was available in order to assess this study in adequate detail as it was presented as a conference abstract only. Furthermore, as this study states it is an update of the analysis completed by Huang et al (2007), it could be assumed that criticisms of Huang et al would still apply. For example, the patient population does not match that of the current decision problem (no prior episode reported) and there is not enough detail provided on how clinical benefits were included in order to reproduce the results of the study.

Ultimately, none of the economic evaluations identified addressed the main outcome in the decision problem, that is, reduction in the recurrence of HE.

D4. **Priority Question:** Appendix 12: Measurement and valuation of health effects

- Please clarify why the search was not updated for the submission.
- Please clarify why this search was only updated in PubMed.

Response

An updated search was conducted to identify relevant HRQL studies pertaining to HE. Please see **Appendix C** for details of the search strategy.

Of the HRQL studies identified in the literature, one utilised the CLDQ assessment. This is the same post-hoc analysis of the RFHE3001 trial by Sanyal et al.

Two trials utilised the SF-36 assessment. Poo et al. collected baseline and end of treatment SF-36 data alongside a 2-week clinical trial of lactulose versus L-ornithine L-aspartate (LOLA) in a Mexican population and Takuma et al. collected baseline and 6-month SF-36 data alongside a clinical trial evaluating zinc versus standard therapy in Japan. Due to SF-36 being a tertiary endpoint and an optional

assessment in RFHE3001, and because data was only available for patients who were in remission, analysis of RFHE3001 SF-36 data was not performed.

Furthermore, the baseline trial populations in the Poo et al. and Takuma et al. studies differed from that of the RFHE3001 trial, in that the former 2 studies enrolled patients with Conn score of 1 or 2, which by definition is more severe that the requirement of Conn score of 0 or 1 in RFHE3001.

No information on adverse events was identified in this systematic literature review.