Norgine Response to NICE Technology Appraisal Committee's Request for Further Analysis on Rifaximin-α 550mg; along with the corresponding revised data - Redacted

Executive Summary

Norgine Pharmaceuticals has undertaken the data analyses requested by the NICE Appraisal Committee at the meeting held on October the 29th 2013 and subsequent second Appraisal Consultation Document issued in November 2013. The Technology Appraisal Committee ('the Committee') requested the following analysis to be undertaken:

- Estimates of utilities from SF-36 quality-of-life data collected from the RFHE3001 trial and mapped directly to the EQ-5D, using all observations in each relevant health state and adjusted for baseline utility,
- Results of scenario analyses reflecting a clinically plausible diminishing mortality benefit with rifaximin-α over time and excluding mortality benefit in the remission state,
- Use of a lifetime time horizon to capture all costs and benefits associated with rifaximin-α and lactulose, and
- Results of a full probabilistic sensitivity analysis for the revised analyses, including the incremental cost-effectiveness ratios.

Based on these requests the company has re-examined the quality of life data recorded in the clinical study report of the RFHE3001 trial. Two measurements of patient quality of life were recorded in this study. Patients were required to complete the chronic liver disease questionnaire (CLDQ) as part of the study protocol. A validated Russian translation version of the CLDQ was not available and therefore this was only recorded in the sub group of patients from North America (USA & Canada). In addition, the SF-36 generic quality of life questionnaire was an optional measurement for patients in this study, so was not recorded in all patients, but *was* available to the Russian cohort of patients in the trial. Using the SF-36 patient data from the study, an SF-12 subset was then used to produce EQ-5D Utility values for application in the model. The data have been presented in both their unadjusted and adjusted form to help understand the nature of the data and the effect of baseline adjustment.

Norgine believe that due to the previously outlined difficulties in recording quality of life in mildly cognitively impaired liver cirrhosis patients that the most appropriate derived utility is that from the disease specific quality of life measure CLDQ. The confidence intervals across all the recording of the SF-36 values compared to those of the CLDQ in the study as outlined in the CSR clearly demonstrate this.

When the methodology requested by the Committee is applied to deriving utility difference for the patients in the study, a result of +0.032 utility gain from use of rifaximin-α vs. placebo in patients receiving a standard of care (91% of patients in both arms were on lactulose) is obtained.

Norgine believe that the more appropriate model inputs are still derived from CLDQ derived utility which resulted in a 0.106 utility gain for patients treated with rifaximin-α vs. placebo in patients receiving a standard of care.

As part of the requested analysis the Committee has required Norgine to produce a lifetime horizon for the economic modelling. Norgine's interpretation of a lifetime horizon is the point at which the last patient in the model dies; in this case 42 years.

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Using the Norgine's basecase assumptions for utility derived from CLDQ at 0.106 Util benefit, and the mortality assumptions based on the RFHE3002 study; the lifetime deterministic ICER is £17,834 per QALY.

Using an assumed incremental utility for rifaximin-α treatment of 0.032 (derived from SF-36 direct adjusted utilities) and the RFHE3002 mortality assumptions; the lifetime deterministic ICER is £29,076 per QALY.

It can be seen from these further analyses that rifaximin-α 550mg is cost effective in either scenario of derived utility.

Norgine has also undertaken a series of scenarios, at the request of the Committee, removing aspects of the mortality assumptions taken in the modelling. The company believe it is important to consider clinical plausibility when examining these sensitivity analyses. A mortality differential does exist in the model which is derived from two simple principles.

> Less time spent at risk from mortality of an HE overt event, as there are simply less events in the rifaximin-α arm.
>
> Fewer patients moving to the second part of the model where a higher mortality risk has been applied as mortality is assumed to be higher after an overt event has occurred.

The company believe these are reasonable clinically plausible assumptions supported by the data. No inherent mortality rate difference is justifiably assumed for rifaximin-α 550mg.

Finally, Norgine have completed both a one-way and a probabilistic sensitivity analysis for the economic model. The results of these analysis together with earlier submitted evidence demonstrate that rifaximin-α 550mg is cost effective in reducing the recurrence of overt episodes of hepatic encephalopathy.

Norgine would again like to highlight the Orr et al publication[1] from the Freeman Hospital, Newcastle-upon-Tyne and the supporting data from Bristol[2] and Ninewells[3] hospitals which has shown consistent reduction in hospitalisations and length of stay through use of rifaximin-α.

Norgine has also completed both a one-way and a probabilistic sensitivity analysis for the economic model. The results of these analysis together with earlier submitted evidence demonstrate that rifaximin-α 550mg is cost effective in reducing the recurrence of overt episodes of hepatic encephalopathy.

Conclusion

The cost effectiveness of rifaximin-α 550mg BD for reduction of recurrence of episodes of overt hepatic encephalopathy has been calculated as the following ICERs, £20,829 (5 years), £19,258 (10 years) and £17,834 (Lifetime – 42 years) in Norgine's basecase CLDQ derived utility and mortality assumptions.

Rifaximin-α 550mg represents a cost effective and potential cost saving option for patients with a high unmet need in a disease area with few therapeutic options.

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Introduction

The response document is structured to respond to the specific requests of the Committee detailed in section 1.2 of the second Appraisal Consultation Document pertaining to the use of Rifaximin-α 550mg for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥18 years of age.

Specifically, the Committee requested the following additional analyses from Norgine, to be submitted by the end of the ACD consultation:

- estimates of utilities from SF-36 quality-of-life data collected from the RFHE3001 trial and mapped directly to the EQ-5D, using all observations in each relevant health state and adjusted for baseline utility,
- results of scenario analyses reflecting a clinically plausible diminishing mortality benefit with rifaximin-α over time and excluding mortality benefit in the remission state,
- use of a lifetime time horizon to capture all costs and benefits associated with rifaximin-α and lactulose, and
- results of a full probabilistic sensitivity analysis for the revised analyses, including the incremental cost-effectiveness ratios.

1 Estimates of utilities from SF-36 data mapped directly to the EQ-5D index

1.1 Background

Norgine's 5 year base case scenario was detailed in the addendum to the original submission, and used utility values derived from a mapping procedure that first converted SF-36 data into an estimated EQ-5D index value, then secondly related EQ-5D values back to *post hoc* analysis of disease-specific QoL, as measured by the Chronic Liver Disease Questionnaire (CLDQ). The motive for this procedure was that there was a published peer-reviewed study from this specific RCT[4] that demonstrated incremental improvement in not only the CLDQ overall score, but also CLDQ domains, and most CLDQ items following treatment with rifaximin vs. standard care. Thus a decision was made to utilise these published data. Exploratory and confirmatory analysis demonstrated convincingly that there was a direct association between the CLDQ and estimated EQ-5D index (Figure 1). In conjunction with observed CLDQ values at baseline, the least-squares mean incremental CLDQ for rifaximin-α in the covert / minimal HE state ('remission'), and observed CLDQ values in the overt state, the mapping procedure was used to estimate corresponding health state utility values.

This approach was Norgine's preferred method because of the problems with using SF-36 derived EQ-5D index values. As previously described, we believe that due to the wide confidence intervals of SF-36 in the RFHE3001 study[5], compared recorded CLDQ, it is correct to use the assumed 0.106 utility benefit for use of rifaximin-α 550mg as our base case scenario, with supporting evidence from alternative scenarios.

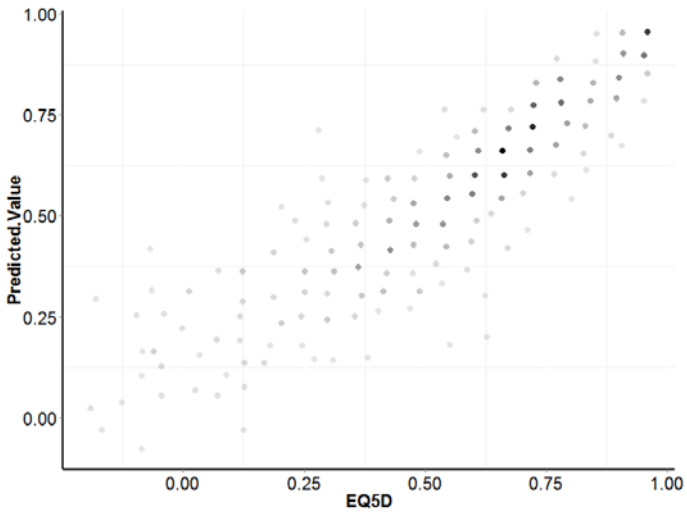

Figure 1. Observed vs. expected EQ-5D values using a model that used the CDLQ

It is important to note that the subjects in the RFHE3001 clinical trial were withdrawn from the trial when they experienced an event. This has had an effect on interpretation of the raw unadjusted quality of life scores described in the CSR. Furthermore, by definition subjects experiencing hepatic encephalopathy were then unlikely to be able to respond adequately to a survey, the company

believe that in this situation it was more appropriate to derive utility from the disease specific measure. Finally, the 30-day recall period for the SF-36 questions could quite possibly be contaminated by subclinical deterioration in those that went on to have an episode of breakthrough HE.

1.2 Methodology

1.2.1 Unadjusted utilities

EQ-5D index utility scores have been calculated from the SF-12 subset of observed SF-36 QoL responses collected during the RFHE3001 study using the response mapping method developed by Grey at al[6]. As the response mapping does not account for missing data, multiple imputation (SPSS 20, IBM Corp, Chicago[7]) was used to impute missing responses to the SF-12.

For a small number of observations, the date of SF-36 data recording suggested these had been collected after the date of breakthrough overt HE and were labelled accordingly and analysed separately from the majority of observations which had been recorded whilst the patients were in the covert / minimal HE state ('remission'). Additionally, analysis of Visit 15 which could include either Month 6 or End-of-Study (EoS) observations, excluded observations which had been made before the scheduled Month 6 window (168 days ± 2 days).

Student's t-test was used to make independent samples comparisons of utility between treatment arms at each of the scheduled study observations in the covert / minimal HE state ('remission').

1.2.2 Baseline adjusted analysis

Change in EQ-5D from baseline was calculated for each discrete time point. Patients with missing baseline values were excluded from the analysis. Only those EQ-5D values recorded during the covert / minimal HE state ('remission'), that is prior to any breakthrough HE episode, were included. Missing values were imputed using linear interpolation between the two nearest neighbouring observed values. Graphical analysis was conducted in Microsoft Excel.

1.3 Results

1.3.1 Unadjusted utilities

At baseline, EQ-5D utility was calculable for 139 placebo patients and 125 rifaximin-α patients. Over the course of the trial, recorded observations in the covert / minimal HE state ('remission') fell steadily until Month 6 when 58 placebo patients (42%) had observable data compared with 78 patients (62%) of the rifaximin-α arm. This is in line with the primary efficacy results.

Figure 2. Unadjusted EQ-5D utilities from RFHE3001 (all observations)

Figure 3. Unadjusted EQ-5D utilities from RFHE3001 (all observations in the covert state)

Figure 2 shows the pattern of unadjusted utilities for all observations. The effect of removing end-of-study observations (those made in the overt state; Figure 3) reveals that during the course of the study, EQ-5D utility in the covert / minimal HE state ('remission') appeared to rise from baseline in the first month for both arms before remaining stable for the remainder. There were no statistically significant differences in the unadjusted utilities between rifaximin-α and placebo at any time point.

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Observations made at the EoS for those patients in the overt state were significantly lower than equivalent EoS observations for patients that remained in the covert state (mean difference 0.168, SEM 0.039; **Error! Reference source not found.**). Subgroup analysis of those who remained in the covert state and subjects who had a breakthrough HE episodes shows that the baseline values for subjects experiencing a BOHE episode was significantly lower than those who remained in the covert state (0.520 vs. 0.596, p=0.013; **Error! Reference source not found.**). For those in which a paired samples comparison was possible the differential in baseline values was somewhat larger at 0.502 vs. 0.616 respectively (**Error! Reference source not found.** & **Error! Reference source not found.**). For subjects who remained in the covert state there was negligible difference between baseline and EoS utility (p=0.647; **Error! Reference source not found.**), however for subjects experiencing an HE episode there was a deterioration in utility of -0.063 (SEM 0.033, p=0.061) from baseline to EoS.

Table 1. Utilities at EoS in the covert and overt states.

Group Statistics

	BRKHE	N	Mean	Std. Deviation	Std. Error Mean
Month 6 / EoS EQ-5D	NO	150	.63089	.234848	.019175
	YES	59	.46312	.257722	.033553

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Month 6 / EoS EQ-5D	Equal variances assumed	2.385	.124	4.521	207	.000	.167768	.037109	.094609	.240927
	Equal variances not assumed			4.341	98.004	.000	.167768	.038645	.091078	.244458

Table 2. Comparison of baseline utility for subjects who did vs. those that did not have an episode of breakthrough HE.

Group Statistics

	BRKHE	N	Mean	Std. Deviation	Std. Error Mean
Baseline EQ-5D	NO	168	.59593	.232598	.017945
	YES	96	.52026	.243064	.024808

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Baseline EQ-5D	Equal variances assumed	.640	.424	2.501	262	.013	.075668	.030251	.016101	.135235
	Equal variances not assumed			2.471	190.727	.014	.075668	.030618	.015275	.136061

Table 3. Paired samples comparison of baseline & Month 6 / EoS utility for subjects who remained in covert state.

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Baseline EQ-5D	.61592	139	.223112	.018924
	Month 6 / EoS EQ-5D	.62365	139	.239076	.020278

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Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Baseline EQ-5D - Month 6 / EoS EQ-5D	-.007734	.198845	.016866	-.041083	.025615	-.459	138	.647

Table 4. Paired samples comparison of baseline & EoS utility for subjects who had a breakthrough HE episode

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Baseline EQ-5D	.50204	54	.235016	.031982
	Month 6 / EoS EQ-5D	.43889	54	.254338	.034611

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Baseline EQ-5D - Month 6 / EoS EQ-5D	.063148	.242358	.032981	-.003003	.129299	1.915	53	.061

1.3.2 Baseline adjusted utilities

Following adjustment for missing data and baseline utility, Figure 4 illustrates the mean change in the estimated EQ-5D index for each scheduled assessment. By Month 6 an incremental difference of 0.032 (SEM 0.0052) favouring rifaximin-α had emerged.

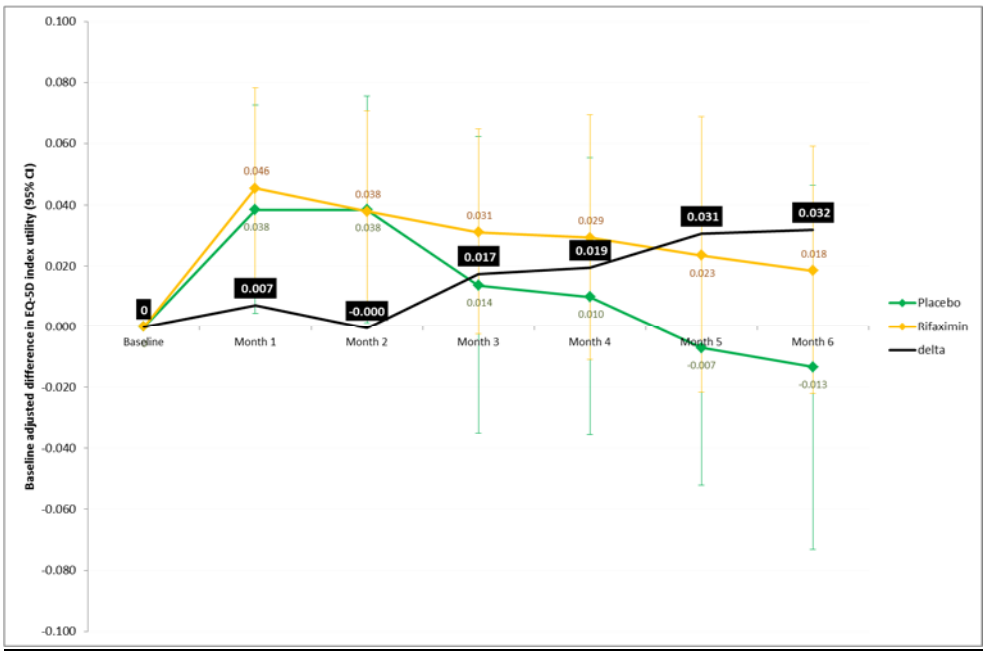

Figure 4. Baseline-adjusted difference in EQ-5D utility at each time point

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1.4 Discussion

There are a number of important issues to consider in relation to direct estimation of health related utility (the EQ-5D index) from the trial-related SF-36 data:

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1. Domains of SF-36 have a much wider variance than CLDQ domains (CSR RFHE3001[5]) suggesting it is a less precise instrument for measuring QoL in this patient population with underlying neurocognitive impairment
2. CLDQ is a disease specific (liver) QOL instrument and SF-36 is a generic QOL instrument. Observed differences in utility derived from disease specific and generic instruments are not unusual across therapy areas and in the pivotal study.
3. SF-36 was an optional instrument in the scheduled assessments whereas CLDQ was a required assessment (in USA and Canada)[5]. Therefore, we it would be expected that this would increase the likelihood of non-random missing data in the SF-36 dataset compared to CLDQ. This indeed was the case:
    - Proportion of patients not completing the questionnaire were [redacted]
    - Proportion of missing values [redacted]
4. Finally, the use of the SF-36 tool has been shown to be of poor quality in patients with cognitive impairment[8] and therefore is a sub-optimal measure of QoL in patients with Hepatic Encephalopathy, who by the very nature of their condition, have significant neurocognitive impairment, throughout the covert / minimal HE ('remission') and overt states.

The above limitations of the SF-36 would not, however, preclude a mapping analysis between CLDQ and Utility derived from SF-36.

Mapping approaches to utility derivation are reasonable as long as the uncertainty associated with the estimate are incorporated appropriately into the modelling exercise (NICE DSU Technical Support Document 10[9]). The two sources of uncertainty inherent in the two-stage mapping of CLDQ to utility have been incorporated in the PSA:

a) the 95% CI of the CLDQ Overall score LS mean benefit for rifaximin-α in the covert / minimal HE state ('remission'); and

b) the 95% CI of the parameter estimate from the repeated measures regression.

The analyses presented in response to the request of the Committee resulted in a difference between rifaximin-α and placebo in the covert / minimal HE state ('remission') which exceeds the minimal clinically important difference for the EQ-5D (≥0.03 units)[10]. Also, this difference in utility whilst being treated with rifaximin-α appeared to be increasing with time.

1.5 Committee-requested Revised Economic Analysis (SF-36 Derived Utility; Scenario 1)

The incremental benefit for rifaximin-α over placebo observed in the baseline-adjusted analysis of EQ-5D change in the covert / minimal HE state ('remission') has been conservatively applied as a constant benefit (despite evidence of an increasing benefit over time) through the lifetime of the patient. In response to concerns over the face-validity of the previous utility for the overt state, and in the absence of observed EQ-5D values in the overt state in RFHE3001, the Conn Score weighted utility decrement from the Standard Gamble study presented in the original Norgine submission was employed. Although observations in the overt state (n=67) were available from the study, the

resulting value of 0.463 is most likely a significant over-estimate since it mainly represented patients with BOHE as defined by Conn Score of 1 plus a 1 grade increase in asterixis and, therefore cannot have represented the utility of patients in Conn Scores 2, 3, or 4. Therefore, it has not been used in the requested scenario analysis. The resultant health state utility values are presented in Table 5. In this scenario, it was assumed that the QoL benefit associated with rifaximin-α treatment would not apply for the first month.

Table 5. Alternative health state utilities based on direct analysis of SF-36 estimated EQ-5D index

		Mean	Lower CI	Upper CI	SEM	N
BASELINE		0.568	0.540	0.597	0.015	264
COVERT1	rifaximin	0.600				
	lactulose	0.568				
OVERT1	rifaximin	0.314				
	lactulose	0.282				
COVERT2	rifaximin	0.600				
	lactulose	0.568				
OVERT2	rifaximin	0.314				
	lactulose	0.282				

	Mean	SE	Lower CI	Upper CI
rifaximin increment	0.032	0.0052	0.022	0.042
SG weighted decrement	0.286			
permanent decrement	-			

Under these assumptions and a five-year model horizon, the deterministic ICER for this scenario is £38,675 per QALY gained. Using a lifetime (42 year) model horizon, the deterministic ICER for this scenario is £38,669 per QALY gained £29,076 per QALY.

1.6 Summary of key findings

- Unadjusted analysis of SF-36 derived utilities observed within the pivotal efficacy found no difference between rifaximin and placebo for patients in the covert / minimal HE state ('remission') .
- In baseline adjusted analysis, correcting for missing values, an increasing incremental utility benefit for rifaximin was observed (+0.032 util at month 6) for patients remaining in the covert / minimal HE state ('remission').
- Applying this incremental benefit for rifaximin to the economic model in addition to a preference-based disutility for time spent in the overt state, the deterministic ICER for rifaximin over a lifetime horizon was £29,076.

2 Reduction in mortality benefit of rifaximin-α over time and exclusion of mortality benefits in the covert / minimal HE state ('remission')

2.1 Background

The Committee expressed concern that under base case assumptions, the mortality benefit for rifaximin-α continues increase throughout the model lifetime whereas the difference in overt HE episodes decreases over time (Figure 5). The following analysis explores whether this holds true over longer model horizons and explores the impact of reducing the indirect mortality benefit on the cost-effectiveness of rifaximin-α.

Figure 5. Health state trajectories for the manufacturer basecase (5 year time horizon)

2.1.1 The Committee's Request

In section 4.12 of the ACD, "*The Committee considered whether it was clinically plausible to expect a differential mortality benefit with rifaximin-α plus lactulose compared with lactulose only. It noted that the manufacturer's updated analysis demonstrated that the time to subsequent overt hepatic encephalopathy episodes decreased as the number of episodes increased. The Committee expressed concern that the model predicted an increasing differential mortality benefit for rifaximin-α when clinical experience indicates decreasing clinical efficacy over time in preventing overt hepatic encephalopathy episodes. The clinical specialist stated that it was plausible that rifaximin-α could have an impact on mortality and the modelled differential seemed reasonable but acknowledged that, with disease progression, the effect in preventing overt hepatic encephalopathy episodes would decrease and that there would be additional causes of death, independent of hepatic encephalopathy, including renal failure, sepsis and bleeding from oesophageal varices. The Committee also noted that the ERG's exploratory analysis indicated a modelled mortality benefit for*

rifaximin-α in the remission state that was independent of the effect in preventing episodes of overt hepatic encephalopathy. The Committee noted from the ERG's exploratory analyses that excluding a differential mortality benefit with rifaximin-α from the remission state increased the ICER to £22,700 per QALY gained and to £30,200 per QALY gained when mortality benefit was excluded from both health states. The Committee concluded that although an initial mortality benefit with rifaximin-α resulting from a reduction in overt hepatic encephalopathy episodes was plausible, the magnitude of the effect is uncertain and the benefit will likely diminish over time with disease progression. It recommended that further analyses be requested excluding mortality benefit in the remission state and incorporating a clinically plausible diminishing mortality benefit over time."

Furthermore in section 4.13 "*The Committee was concerned about the incremental benefit with rifaximin-α in the remission state and the increasing mortality benefit with disease progression.*" requesting further analyses be conducted including "*Results of scenario analyses reflecting a clinically plausible diminishing mortality benefit with rifaximin- α over time and excluding mortality benefit in the remission state*."

2.1.2 Norgine Response to ACD Section 4.13:

Norgine sought additional clarification from NICE's Technical Team on how to address the committee's request in a rational and clinically plausible manner. It was felt that there may be a potential misunderstanding of the way that mortality is derived in the model that may have led to this request. It was felt that Norgine's clarification on this may help address the committee's concerns.

Norgine believes the Committee's perception of the incremental benefit with rifaximin-α in the covert / minimal HE state (*'remission'*) and the increasing mortality benefit with disease progression, is an artefact of taking a short term view of the model outputs. Taking a longer term view, consistent with the Committee's request to use a life time horizon, revised model outputs demonstrating that there is a clinically plausible diminishing mortality benefit within the previously submitted model are presented in Figure 6

Figure 6. Absolute difference in mortality between treatment arms for different scenarios (10 year time horizon)

The model inputs for mortality in the four health states C_1, C_2, O_1 and O_2, are the same for the rifaximin-α and lactulose cohorts. No explicit differential mortality benefit is included in the model.

Differences in mortality in both the covert / minimal HE ('remission') and overt states derive from the reduction in episodes of overt HE provided by rifaximin-α treatment.

In the covert / minimal HE state ('remission'), mortality inputs were obtained by using the best-fit parametric proportional hazards survival models from RFHE3002. In the C_1 state this was found to a log normal distribution and Weibull for C_2 (Figure 7). Mortality risk was found to be higher in the C_2 state than in C_1. An increasing risk of mortality after each HE event is clinically and statistically plausible.

Firstly, each breakthrough HE episode marks a deterioration in underlying liver disease status and will exerts systemic effects from which the patient may not fully recover. This has been clearly established for cognitive function where patients do not fully return to pre-episode levels[11].

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Figure 7. Fitted survival functions from RFHE3002 covert (C_1) and subsequent covert (C_2) states.

Additionally, it is important to recognise that, as modelled, the first observed and subsequent covert / minimal HE state ('remission') have considerably different processes that contribute to their differential modelled mortality. In the RFHE3002 study, study participants entered the study with a mean duration of 'remission' (remaining in the covert state) of 133 days. Our understanding of survival following HE is informed by Bustamante[12] (Figure 8) showing that hazard of death is highest within the first three months following HE. The model assumption of full recovery after 30.4 days following a breakthrough HE episode, means that patients re-enter a subsequent covert state (C_2) at an elevated risk of mortality than when they first entered the model in the first observed covert state (C_1). It is not plausible to assume that on "recovery" from any overt state after 30 days (first or subsequent), patients would automatically return to their initial baseline hazard of death on entering the model. Therefore it is reasonable to assume that the composite subsequent covert state modelled would incorporate this excess risk which is attributable to HE events themselves. Therefore an indirect mortality benefit for rifaximin arising from avoidance of transition from C_1 to C_2 is clinically reasonable.

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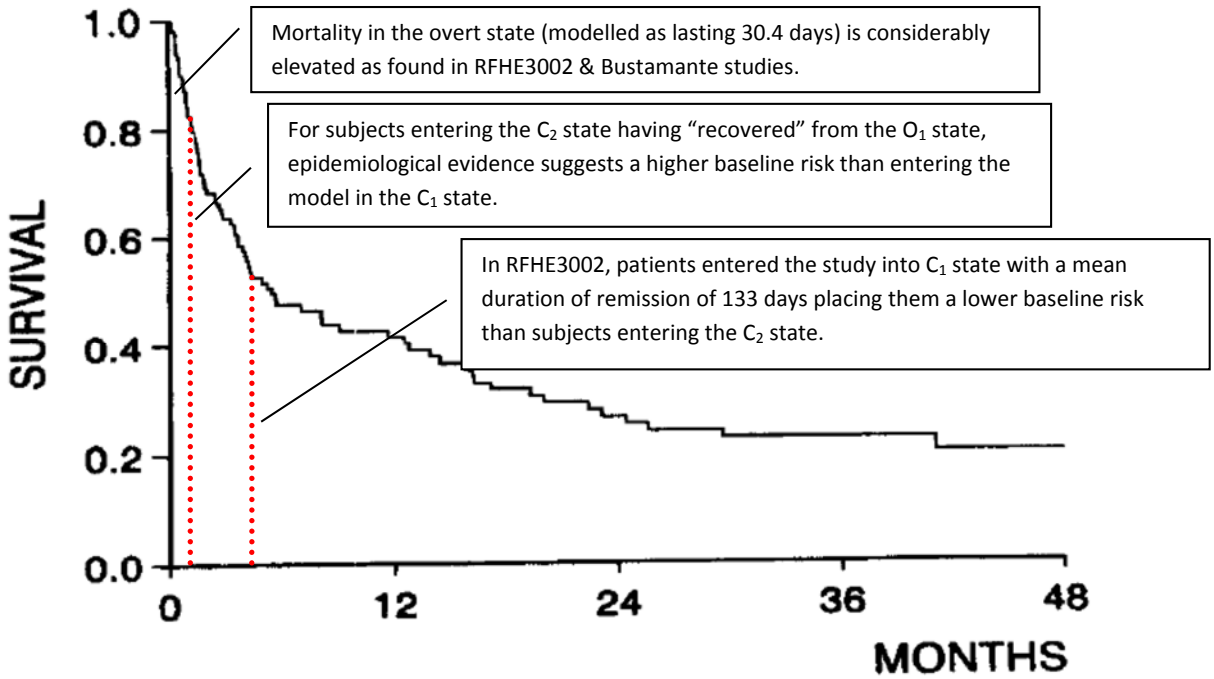

Figure 8. Contribution of differential survival to modelled mortality in the covert and overt states (after Bustamante[12]).

As these risks were applied to both cohorts in the model it is clear that no direct differential mortality was assumed. Differences in mortality arise from the reduction in HE episodes in the rifaximin-α group by two mechanisms:

1) avoidance of the acute 30-day mortality associated with O_1 and O_2; and
2) longer retention in the C_1 state with exposure to a lower hazard of death than equivalent cases who transition to the C_2 state having recovered from O_1.

Both mechanisms contributing to accrued mortality benefit for rifaximin are clinically plausible.

2.2 Methods

As requested, Norgine have explored alternative economic model scenarios to evaluate the impact of the indirect mortality benefit for rifaximin-α 550mg.

2.2.1 Setting C2 mortality to equal C1 mortality (Scenario 2)

[No increase in mortality risk after BOHE cf. before BOHE]

One consequence of transition to the O_1 state, for those that 'recover', is exposure to a higher observed mortality rate in the composite C_2 state. As illustrated, this is likely to incorporate the residual excess hazard of mortality following an overt HE episode. In order to test the impact of this assumption on the cost-effectiveness of rifaximin Scenario 2 sets the C_2 mortality rate to that of the C_1 state.

2.2.2 Setting overt mortality to be equal to covert / minimal HE mortality (Scenario 3)
[No increase in mortality risk upon entering an overt HE episode]

The other source of indirect mortality benefit for rifaximin is the high probability of mortality experienced during overt episodes. In order to test the impact of this assumption on the cost-effectiveness of rifaximin Scenario 3 sets the O_1 mortality probability to that of the equivalent C_1 state, and O_2 mortality probability to that of the equivalent C_2 state.

2.2.3 Combining Scenario 2 and Scenario 3 (Scenario 4)
[Mortality is not affected by breakthrough overt episodes]

In this scenario, mortality benefit for rifaximin is reduced to zero throughout the model.

2.3 Results

With regard to the Committee's request for analysis incorporating a clinically plausible diminishing mortality benefit over time, Norgine provide the following evidence that such an effect exists within the current model. Extending the model to a lifetime horizon (42 years) illustrates that the absolute difference in mortality between rifaximin and placebo ultimately decreases in all scenarios (excluding Scenario 4) as illustrated in Figure 6.

2.3.1 Setting C_2 mortality to equal C_1 mortality (Scenario 2)

From a 5-year base case of £20,829, application of Scenario 2 (Figure 9) produces a deterministic ICER of £23,133 per QALY.

2.3.2 Setting overt mortality to be equal to covert / minimal HE mortality (Scenario 3)

Application of Scenario 3 (Figure 10) produces a deterministic ICER of £25,221 per QALY.

2.3.3 Combining Scenario 2 and Scenario 3 (Scenario 4)

Application of Scenario 4 (Figure 11) produces a deterministic ICER of £30,238 per QALY.

Figure 9. Health state trajectories for Scenario 2 where C_2 mortality equals C_1 mortality

Figure 10. Health state trajectories for Scenario 3 where Overt mortality equals Covert mortality

Figure 11. Health state trajectories for Scenario 4 (combining Scenarios 2 & 3)

2.4 Discussion

- The existing model structure incorporates a clinically plausible diminishing mortality benefit over the lifetime model horizon requested.
- The modelled mortality benefit for rifaximin-α 550mg is clinically plausible and arises from avoiding both the acute (30-day) and sub-acute (30-day to 3-month) excess hazard of death associated with BOHE episodes.
- Evidence of causality between HE episodes and increased mortality is well-documented, casting doubt on the clinical plausibility of scenario analysis which sets overt mortality to that of the equivalent covert state (O_1=C_1 and O_2=C_2).
- Exclusion of this benefit in sensitivity analysis reveals that rifaximin-α 550mg would still be cost-effective at the upper limit of NICE willingness-to-pay threshold.

3 Use of Lifetime Horizon

At 42 years, the percentage of patients remaining alive in the rifaximin arm of the model falls below 0.1%, effectively setting the limit of the lifetime horizon.

Using the Norgine basecase, the lifetime deterministic ICER falls to £17,834 per QALY.

Under Scenario 1 (reduced incremental utility for rifaximin-α 550mg treatment), the lifetime deterministic ICER is £29,076 per QALY.

Under Scenario 2 (C_2 mortality equal to C_1 mortality), the lifetime deterministic ICER is £21,952 per QALY.

Under Scenario 3 (Overt mortality equal to Covert mortality), the lifetime deterministic ICER is £21,797 per QALY.

Under Scenario 4 (reduced incremental utility for rifaximin-α 550mg treatment), the lifetime deterministic ICER is £31,887 per QALY.

4 One-way Sensitivity Analysis

Figure 12 below represents the one way sensitivity analysis for the Norgine basecase cost effectiveness analysis in a tornado diagram. The utility assumption based on the LS mean CLDQ Overall score incremental benefit for rifaximin is the most influential variable on the ICER.

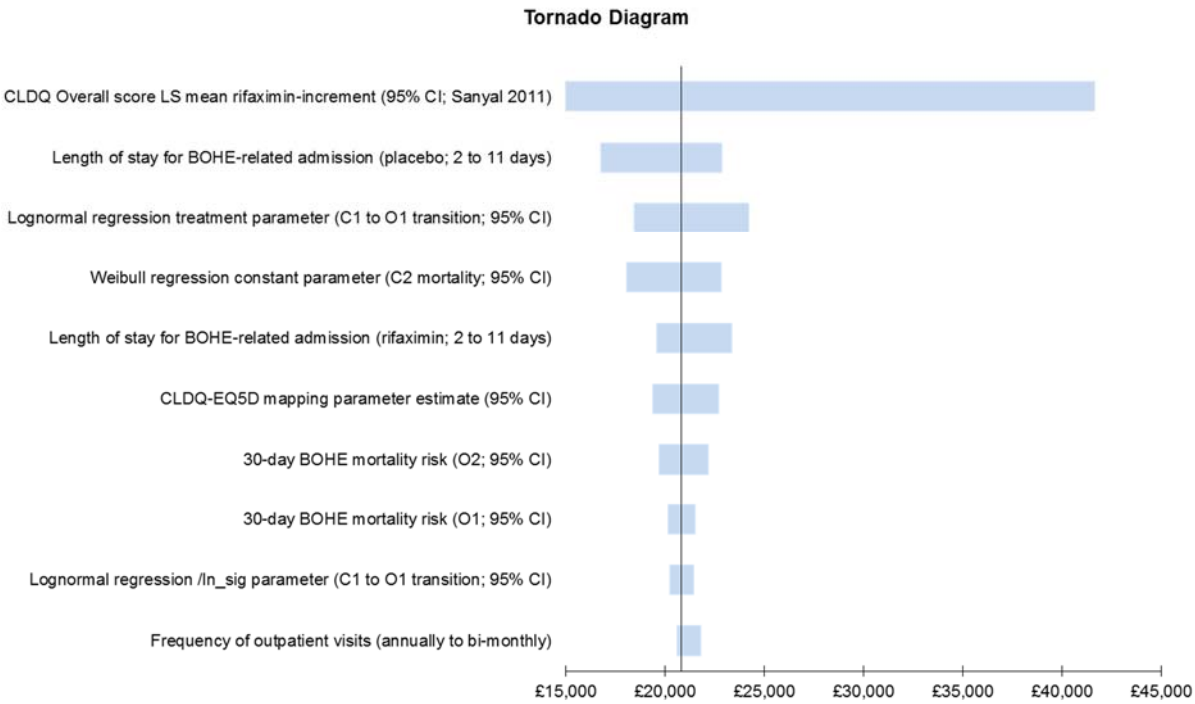

Figure 12. One-way sensitivity analysis for Norgine basecase (5-year horizon)

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5 Probabilistic Sensitivity Analysis (PSA)

All probabilistic sensitivity analyses are based on 10,000 simulations for each scenario. The range of uncertainty for each parameter is described in Table 6. All parameters are varied within their respective stated limits using random sampling from a distribution appropriate to each parameter. The survival functions are varied according to multivariate normal distributions specified by their respective variance-covariance matrix.

5.1 Norgine basecase

The PSA for the Norgine basecase (5-year horizon) indicates that at the upper limit of NICE willingness to pay of £30,000 per QALY, rifaximin-α 550mg has a 85.5% probability of being cost-effective (Figure 13). The probabilistic ICER is £20,798 per QALY compared to a deterministic ICER of £20,832 per QALY.

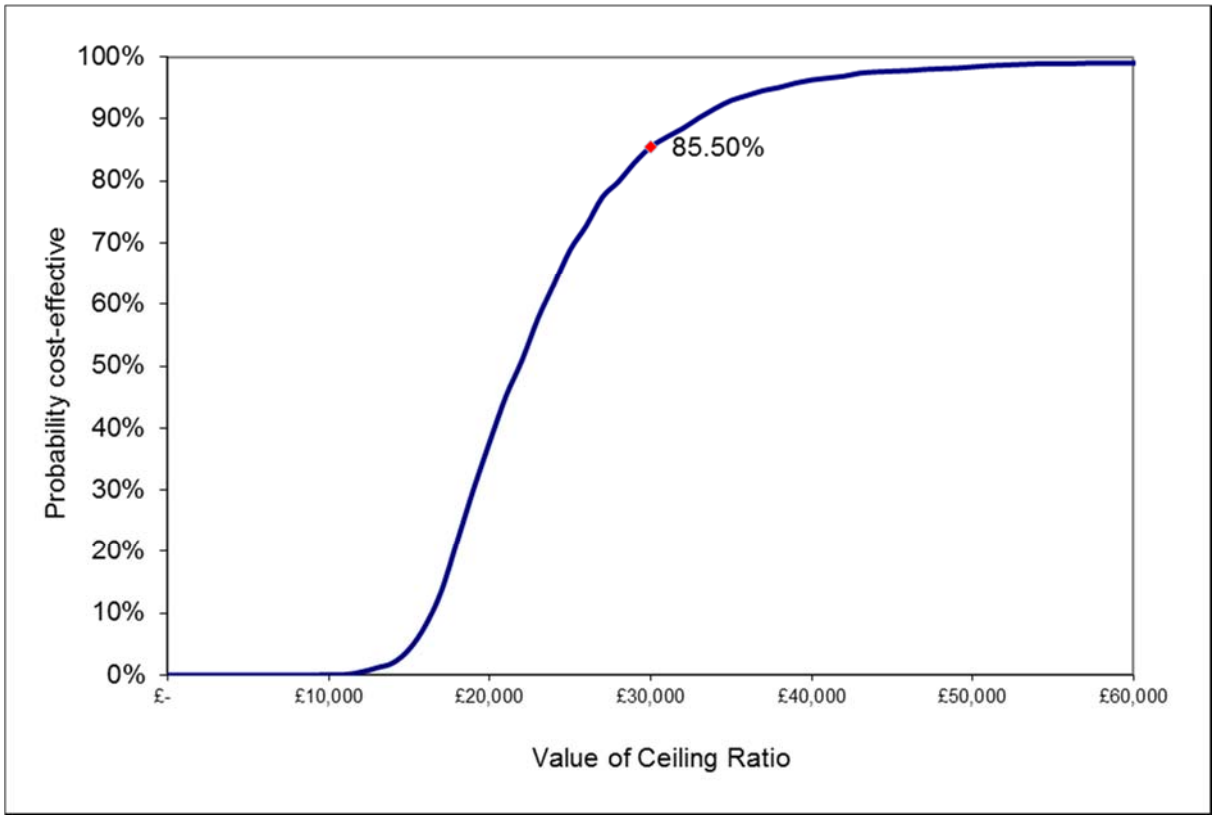

Figure 13. Cost-effectiveness acceptability curve (CEAC) for Norgine basecase

5.1.1 Norgine basecase with a Lifetime Horizon

The PSA for a modified Norgine basecase with a lifetime (42yr) horizon indicates that at the upper limit of NICE willingness to pay of £30,000 per QALY, rifaximin-α 550mg has a 95.5% probability of being cost-effective (Figure 14). The probabilistic ICER is £18,144 per QALY compared to a deterministic ICER of £17,826 per QALY.

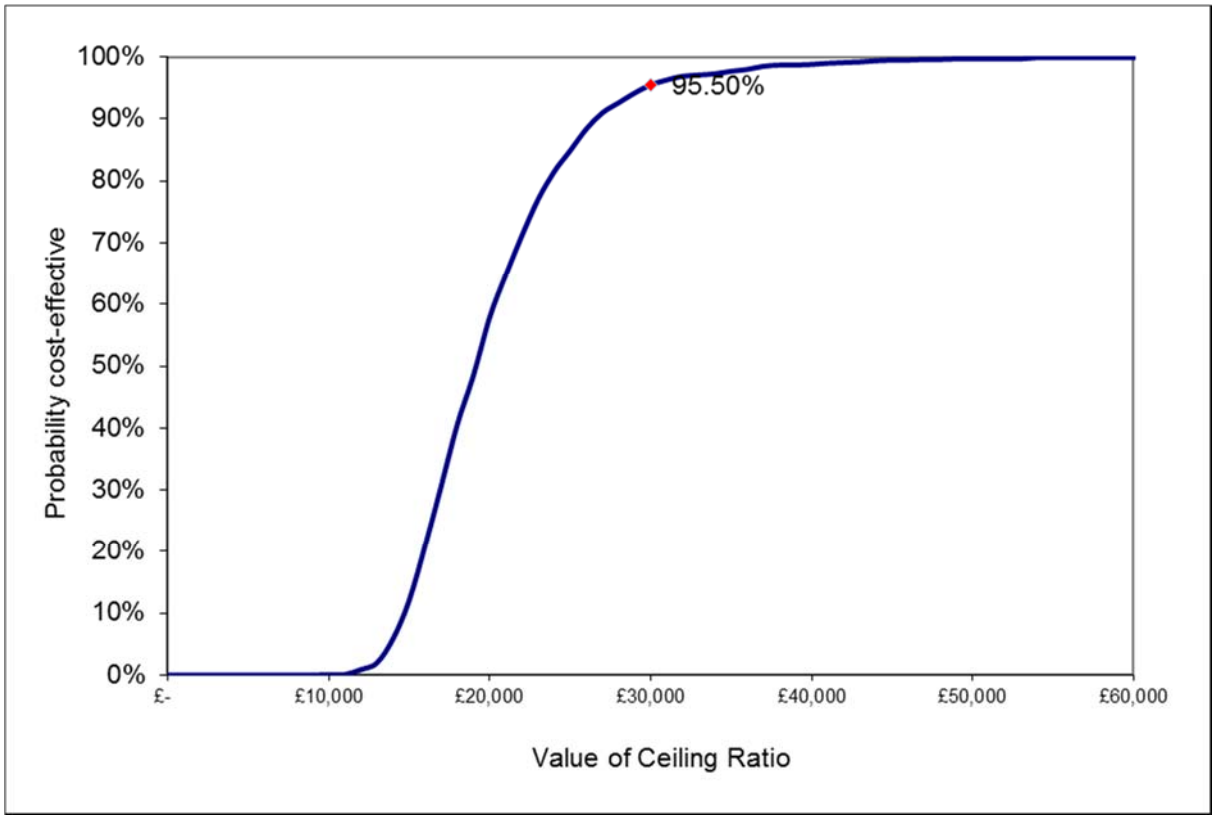

Figure 14. CEAC for modified Norgine basecase with lifetime horizon.

5.2 Scenario 1 with lifetime horizon (SF-36 derived utility)

The PSA for the sensitivity analysis scenario requested based on utility data from the baseline-adjusted SF-36-derived utility analysis with a lifetime (42 year) horizon indicates that at the upper limit of NICE willingness to pay of £30,000 per QALY, rifaximin-α 550mg has a 46.4% probability of being cost-effective (Figure 15). The probabilistic ICER is £29,668 per QALY compared to a deterministic ICER of £29,063 per QALY.

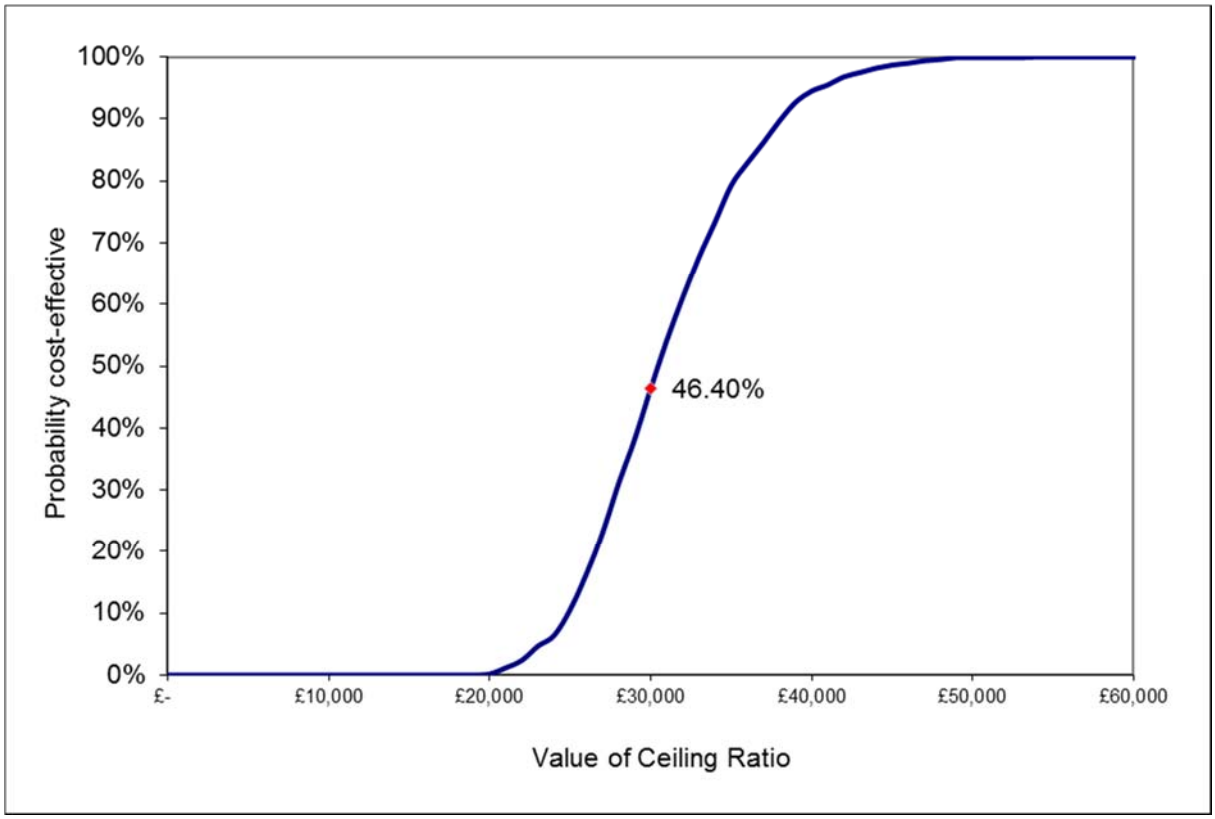

Figure 15. CEAC for NICE reference case (reduced incremental utility with lifetime horizon).

5.3 Scenario 2 with lifetime horizon

The PSA for the Scenario 2, setting C_2 mortality to the same function as C_1 within the Norgine basecase using a 42 year horizon indicates that at the upper limit of NICE willingness to pay of £30,000 per QALY, rifaximin-α 550mg has a 79.2% probability of being cost-effective (Figure 16). The probabilistic ICER is £22,324 per QALY compared to a deterministic ICER of £21,955 per QALY.

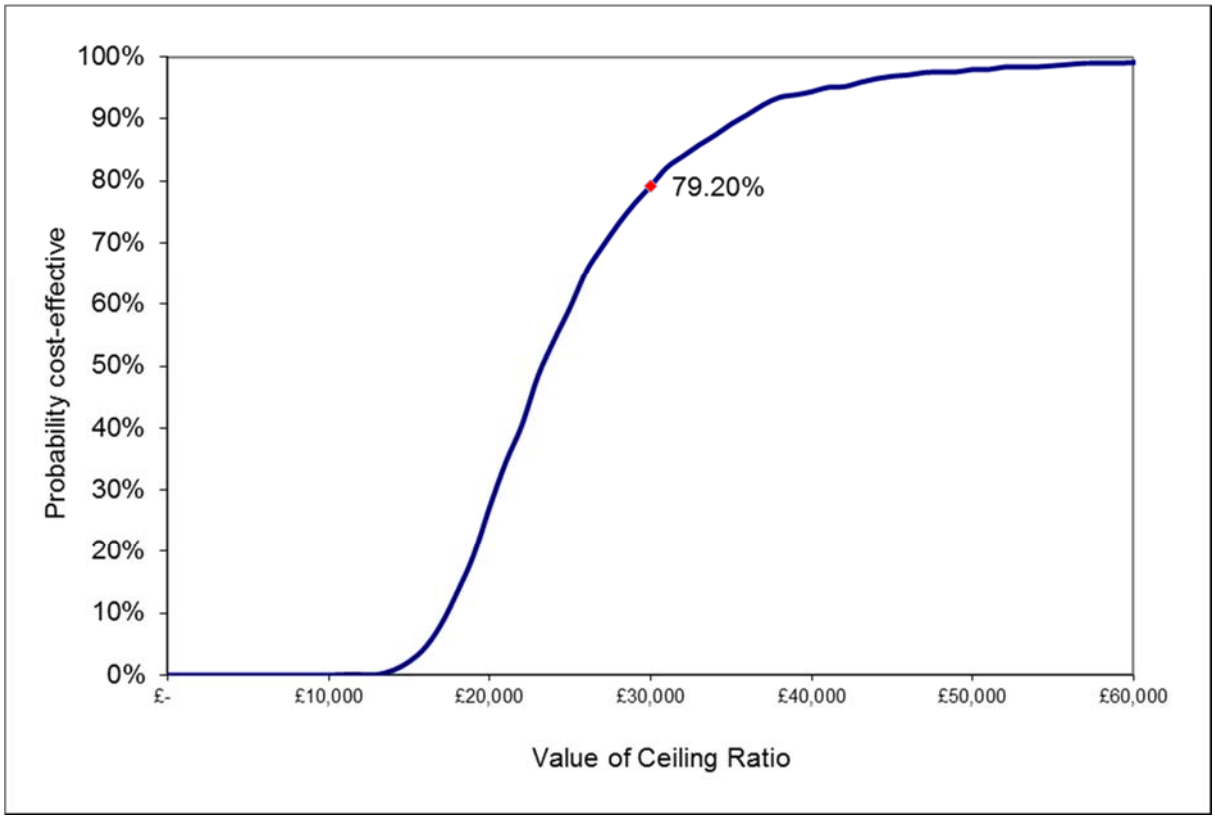

Figure 16. CEAC for Scenario 2; C2 mortality equal to C1 mortality within Norgine base case

5.4 Scenario 3 with lifetime horizon

The PSA for the Scenario 3, setting overt mortality to their respective covert mortality within the Norgine basecase using a 42 year horizon indicates that at the upper limit of NICE willingness to pay of £30,000 per QALY, rifaximin-α 550mg has a 80.6% probability of being cost-effective (Figure 17). The probabilistic ICER is £22,111 per QALY compared to a deterministic ICER of £21,800 per QALY.

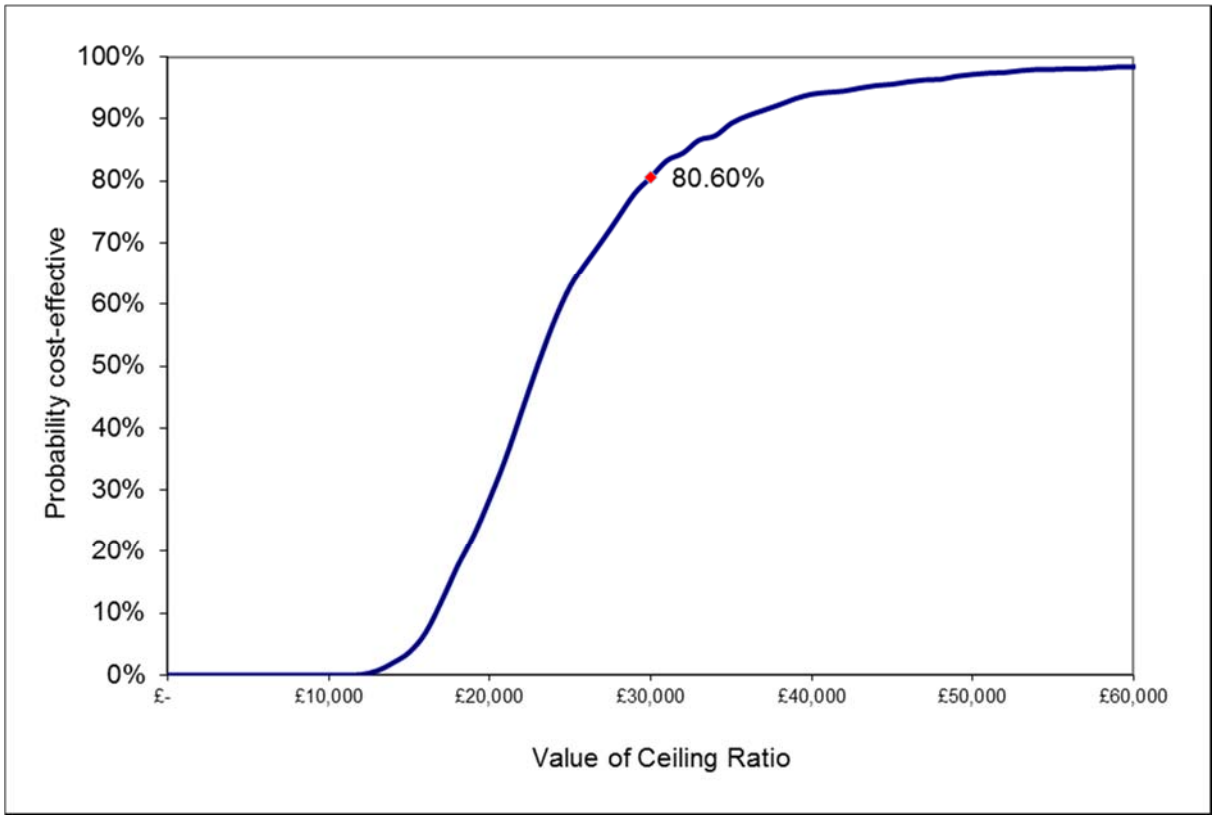

Figure 17. CEAC for Scenario 3 (overt mortality equal to covert mortality within Norgine base case)

5.5 Scenario 4 with lifetime horizon

The PSA for the Scenario 4, combining Scenarios 2 & 3 within the Norgine basecase using a 42 year horizon indicates that at the upper limit of NICE willingness to pay of £30,000 per QALY, rifaximin-α 550mg has a 37.1% probability of being cost-effective (Figure 18). The probabilistic ICER is £32,420 per QALY compared to a deterministic ICER of £31,916 per QALY.

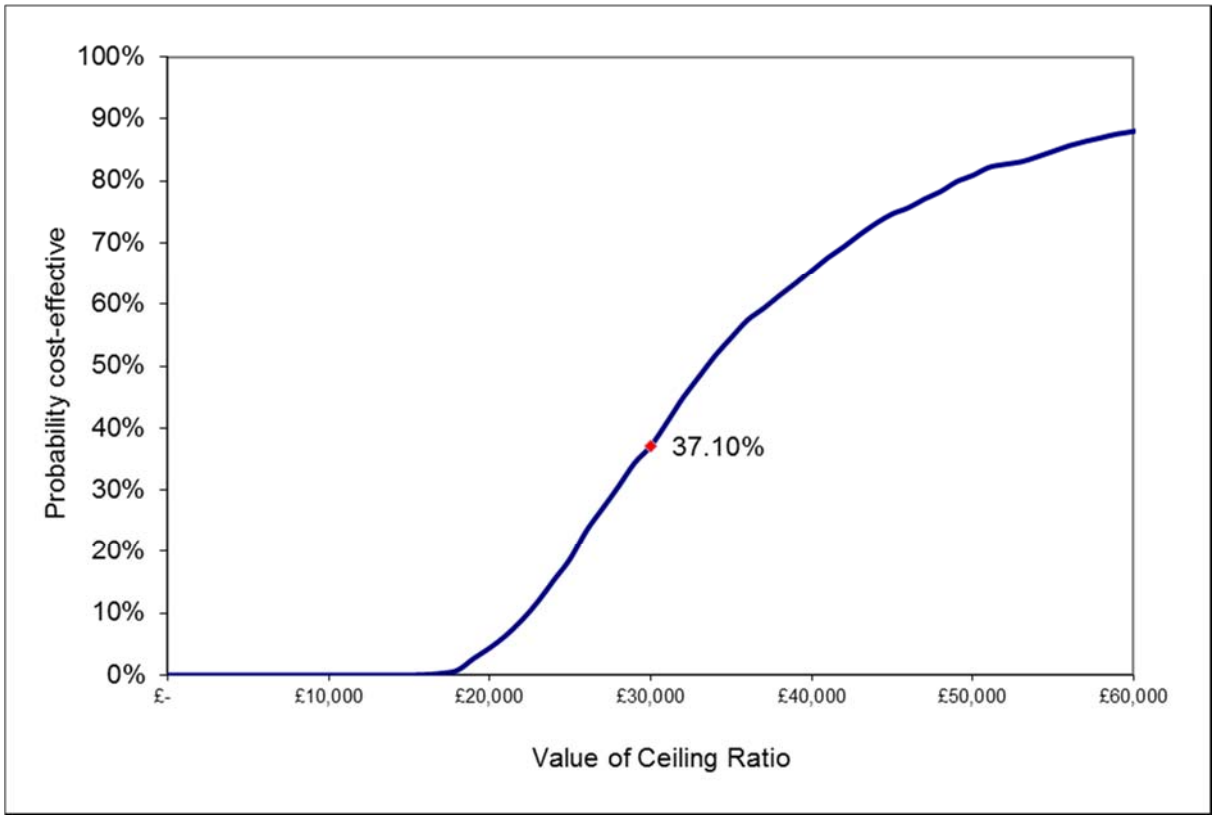

Figure 18. CEAC for Scenario 4 (no mortality benefit for rifaximin-α)

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Table 6. List of parameters varied in the probabilistic sensitivity analyses (shaded cells used in Scenario 1 only; MVN = multivariate normal)

Variable	Default value	Lower limit	Upper limit	Distribution	Reference for value	Reference for uncertainty
Average daily dose of lactulose (mL) - placebo arm	52.65	52.25	53.05	Normal	RFHE3001 (Rivotal trial)	+/- 95% CI estimated from std error
Average daily dose of lactulose (mL) - rifaximin arm	47.10	46.75	47.45	Normal		
Rifaximin tablet price	£4.63	4.63	4.63	None	BNF December 2013 - rifaximin 550mg, net price 56-tab pack = £259.23	Not varied
Lactulose price (500 mL)	£3.11	3.11	3.11	None	BNF December 2013 - Net price 500-mL=£3.11	Not varied
Cost of outpatient visit	£176.27	£176.10	£176.44	Gamma	Department of Health. NHS Reference costs 2011	+/- 95% CI estimated from std error
Frequency of outpatient visits	3.00	1.00	6.00	Gamma	KOL ad-board	KOL opinion
Liver Failure Disorders with Interventions	£2,028.42	£1,780.53	£2,276.32	Gamma	Department of Health. NHS Reference costs 2011	+/- 95% CI estimated from std error
Liver Failure Disorders without Interventions	£3,988.26	£3,881.85	£4,094.67	Gamma		
Non-Malignant Liver Disorders with Catastrophic CCs	£3,084.07	£2,796.19	£3,371.94	Gamma		
Non-Malignant Liver Disorders with Severe CCs	£2,421.08	£2,219.31	£2,622.85	Gamma		
Non-Malignant Liver Disorders with Major CCs	£1,795.26	£1,694.55	£1,895.98	Gamma		
Non-Malignant Liver Disorders without Major CCs	£1,795.26	£1,715.41	£1,875.12	Gamma		
Percentage hospitalised following BOHE - aggregate (ITT)	52.88%	39.50%	63.10%	Beta	RFHE3001 (Rivotal trial)	+/- 95% CI estimated from std error
Length of stay (placebo)	5.00	2.00	11.00	Gamma	KOL opinion	KOL opinion
Length of stay (rifaximin)	5.00	2.00	11.00	Gamma		
EQ-5D population norm (all population)	0.94	0.93	0.95	Normal	Paul Kind, Hardman G, & Macran S. CHE discussion paper 172: UK Population Norms for EQ-5D. 1999	+/- 95% CI estimated from std error
EQ-5D population norm (population aged <25)	0.93	0.92	0.94	Normal		
EQ-5D population norm (population aged 25-34)	0.91	0.90	0.92	Normal		
EQ-5D population norm (population aged 35-44)	0.85	0.84	0.86	Normal		
EQ-5D population norm (population aged 45-54)	0.80	0.76	0.84	Normal		
EQ-5D population norm (population aged 55-64)	0.78	0.76	0.80	Normal		
EQ-5D population norm (population aged 65-74)	0.73	0.71	0.75	Normal		
EQ-5D population norm (population aged 75+)	0.73	0.70	0.76	Normal		
Duration of episode (utility) - lactulose	11.00	1.00	30.00	Gamma	KOL ad-board	Assumption
Duration of episode (utility) - rifaximin	11.00	1.00	30.00	Gamma		
Lognormal regression constant parameter (covert mortality)	5.3616	4.3763	6.3469	MVN	RFHE3002 survival analysis	95% CI taken from STATA regression
Lognormal regression /ln_sig parameter (covert mortality)	0.6471	0.3271	0.9672	MVN		
Probability of mortality within 31 days of 1st BOHE	0.1100	0.0570	0.1630	Beta	RFHE3002 observed proportions	+/- 95% CI estimated from std error
Weibull regression constant parameter (sub-covert mortality)	-3.6201	-4.3593	-2.8810	MVN	RFHE3002 survival analysis	95% CI taken from STATA regression
Weibull regression /ln_sig parameter (sub-covert mortality)	0.8002	0.5636	1.1362	MVN		
Probability of mortality within 31 days of subsequent BOHE	0.0770	0.0394	0.1146	Beta	RFHE3002 observed proportions	+/- 95% CI estimated from std error
Lognormal regression treatment parameter (covert HE)	1.0944	0.5679	1.6210	MVN	RFHE3001 survival analysis	95% CI taken from STATA regression
Lognormal regression constant parameter (covert HE)	1.7959	1.4496	2.1422	MVN		
Lognormal regression /ln_sig parameter (covert HE)	0.6235	0.4739	0.7731	MVN		
Lognormal regression treatment parameter (sub-covert HE)	-1.0944	-1.6210	-0.5679	MVN	RFHE3002 survival analysis	95% CI taken from STATA regression
Lognormal regression constant parameter (sub-covert HE)	1.3830	0.9924	1.7736	MVN		
Lognormal regression /ln_sig parameter (sub-covert HE)	0.5533	0.3686	0.7380	MVN		
CLDQ-EQ5D conversion factor	0.143	0.131	0.154	Normal	RFHE3001 post-hoc analysis	95% CI taken from SPSS GEE regression
CLDQ rifaximin-increment	0.743	0.182	1.303	Normal	Sanyal A et al. Aliment Pharmacol Ther 2011;34(8):853–61	95% CI taken from LS mean estimate
SF-36 baseline utility	0.568	0.541	0.599	Beta	RFHE3001 post hoc analysis	95% CI taken from SPSS descriptives
SF-36 baseline-adjusted rifaximin-utility increment	0.032	0.018	0.038	Normal		
SG utility for Conn Score 0	0.915	0.8763	0.9537	Beta	SG values from Norgine commissioned study	+/- 95% CI estimated from std error
SG utility for Conn Score 1	0.837	0.7858	0.8882	Beta		
SG utility for Conn Score 2	0.683	0.6185	0.7475	Beta		
SG utility for Conn Score 3	0.489	0.4197	0.5583	Beta		
SG utility for Conn Score 4	0.215	0.1581	0.2719	Beta		
Percentage of patients with Conn score 0 at baseline (ITT)	66.89%	61.56%	72.22%	Beta	RFHE3001 (Rivotal trial)	+/- 95% CI estimated from std error
Percentage of patients with Conn score 1 at first episode (ITT)	16.00%	8.81%	23.19%	Beta		
Percentage of patients with Conn score 2 at first episode (ITT)	52.00%	42.21%	61.79%	Beta		
Percentage of patients with Conn score 3 at first episode (ITT)	22.00%	13.88%	30.12%	Beta		
Percentage of patients with Conn score 4 at first episode (ITT)	3.00%	0.00%	6.34%	Beta		

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Appendix I: Supplementary Analyses Suggested in the ERG Critique of Norgine Addendum to the NICE STA on Rifaximin-α 550mg.

This material is supplied in an accompanying document [Supplementary Analyses Suggested in the ERG Critique of Norgine Addendum to the NICE STA on Rifaximin-α 550mg.doc].

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