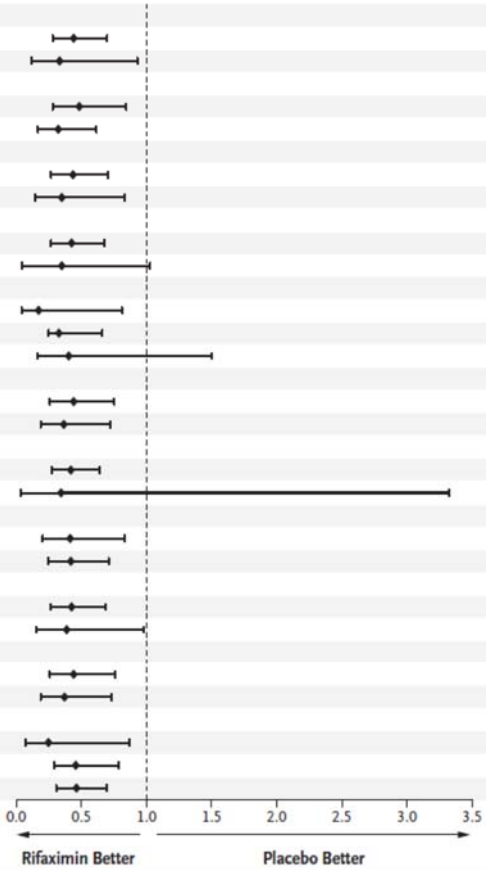
Norgine Response to 2nd NICE ACD Consultation on Rifaximin–α 550mg_Redacted

No	ACD Section & Page Number	Relevant Text	Norgine's Comments
1.	Section 3.6 Page 8	The manufacturer also stated that there were no consistent differences between the rifaximin-α and placebo groups in change from baseline using the SF-36 and Epworth Sleepiness Scale.	• SF-36 and Epworth Sleepiness Scale were optional assessments and tertiary endpoints within the study (please see page 44 and 45 of the original submission) and measured changes from baseline to End of Study (EoS). • It is also worth considering that the study design with respect to the QoL endpoints may have been flawed, in that comparing baseline and EoS assessment scores may not be the most appropriate way to capture differences in QoL in this patient group. A time weighted methodology appears to be more appropriate. • Please see Norgine Response to ACD Section 3.32, 4.3, 4.8 and 4.9 (below)
2.	Section 3.7 page 8-9	Section 3.7 Page 8-9	Norgine suggests the following text be added to the end of section 3.7 for clarity "This was primarily due to low patient numbers in these sub-groups."
3.	Section 3.19 Page 16	The manufacturer used the aggregated 6-month probability rather than individual probabilities of 61.29% for rifaximin-α and 49.32% for placebo on the basis that <u>the rates of hepatic encephalopathy hospital admissions in the trial were not statistically significantly different between the 2 arms.</u>	**Factual inaccuracy** Use of the word 'rates' is incorrect in this context. Rifaximin-α 550mg reduces the rate of hospitalisation due to HE compared to placebo. This was demonstrated clearly as a secondary endpoint of the pivotal study RFHE3001. Fewer patients in the rifaximin-α group (19/140) were hospitalised than the placebo group (36/159) - hazard ratio of 0.50 (95% CI, 0.29 to 0.87; P = 0.01).
4.	Section 3.20 Page 17	It then carried out regression analysis to derive the relationship between overall CLDQ scores from RFHE3001 and EQ-5D utility, which showed that 59% of the variation in the predicted EQ-5D utility was explained by the overall CLDQ score. The manufacturer also carried out a repeated measures analysis to quantify the relationship. The resulting parameter estimate for CLDQ was	**Factual inaccuracy** The percentage variance explained (R-squared=0.59; or 59% as reported) refers to exploratory curve-estimation analysis which did not account for repeated observations within subjects. This analysis itself was not used to derive the relationship between CLDQ Overall score and EQ-5D utility but to determine the possible shape of any relationship in order to inform the choice of repeated measures model. As a linear curve was found to be a good fit to the relationship a General Linear Mixed Modelling approach to repeated measures analysis was selected using untransformed EQ-5D score as the dependent variable and untransformed CLDQ Overall score as a continuous covariate. In the resulting GLMM analysis, CLDQ was a highly significant predictor (p<0.001) of EQ-5D, with

		applied to the baseline CLDQ score, the increment in the CLDQ score for the rifaximin-α arm while in remission and the CLDQ scores for the overt state.	little unexplained variance between observed utility score and those predicted by CLDQ (R-squared = 0.835). The strength of this association suggests that liver-related morbidity may explain the majority of differences in health-related utility in these subjects.
5.	Section 3.23 Page 19	The ERG identified a 6-month trial of rifaximin-α compared with neomycin reported by Miglio et al. (1997) which was not presented in the manufacturer's submission. The ERG acknowledged the manufacturer's justification for excluding the study. However, it remained concerned about excluding neomycin from the analysis because clinical expert opinion indicated that it works in the same way as rifaximin-α and is sometimes used in clinical practice, especially for people not having a liver transplant, even though it is not as well tolerated as rifaximin-α.	Use of neomycin in this indication is exceptional in UK clinical practice as evidenced by clinical expert opinion expressed at both committee meetings and in comments from consultees who did not agree that it would be a suitable comparator for this appraisal. Whilst the scope included neomycin this agent is rarely if ever used due to toxicity. Including this section in the guidance introduces inconsistency since in section 4.1 the Committee concluded that neomycin was not an appropriate comparator. ACD Section 4.1 *'The clinical specialists also stated that neomycin was not used routinely in clinical practice because of the significant toxicity associated with its long-term use. In particular, its association with deafness made it an unacceptable alternative. The Committee recognised the need for alternative treatment options in maintaining remission from episodes of hepatic encephalopathy and also concluded that neomycin was not an appropriate comparator for this appraisal'*
6.	Section 3.24 Page 20	The ERG was concerned about the validity of this assumption, given that the treatment effect of rifaximin-α compared with placebo was not statistically significant in the subgroup with MELD scores of 19 to 24 (the more severe MELD score category in the trial). In addition, it noted that the study by Hassest et al. (2001), which was provided as evidence for the effectiveness of rifaximin-α in patients with MELD scores of 20 or more, was a poor quality descriptive study.	This was addressed at the last committee meeting where the clinical expert present validated this assumption as the primary reason that these subgroups didn't reach significance is due to the very small number of patients in these subgroups – the effect is still trending in the direction favouring rifaximin and is consistent with other subgroups. The concern of the ERG is not substantiated by the evidence. Figure 3 of the Bass et al clearly indicates that the mean effect favouring rifaximin in subgroup with the highest MELD scores is well within the confidence limits of the two more populous subgroup with lower MELD scores. That it does not achieve statistical significance is entirely to be expected from the very small numbers of patients available. The Hassest study, whilst being descriptive does provide some evidence of effect in patients with a high MELD score. It is also worthy of note that patients with MELD score ≥20 are more difficult to study for a number of reasons, including the ethical and practical constraints of assessing and studying patients with

severe liver disease who are often close to the end of their life and thus may not complete the study .

Please see below for Figure 3 from the Bass et al

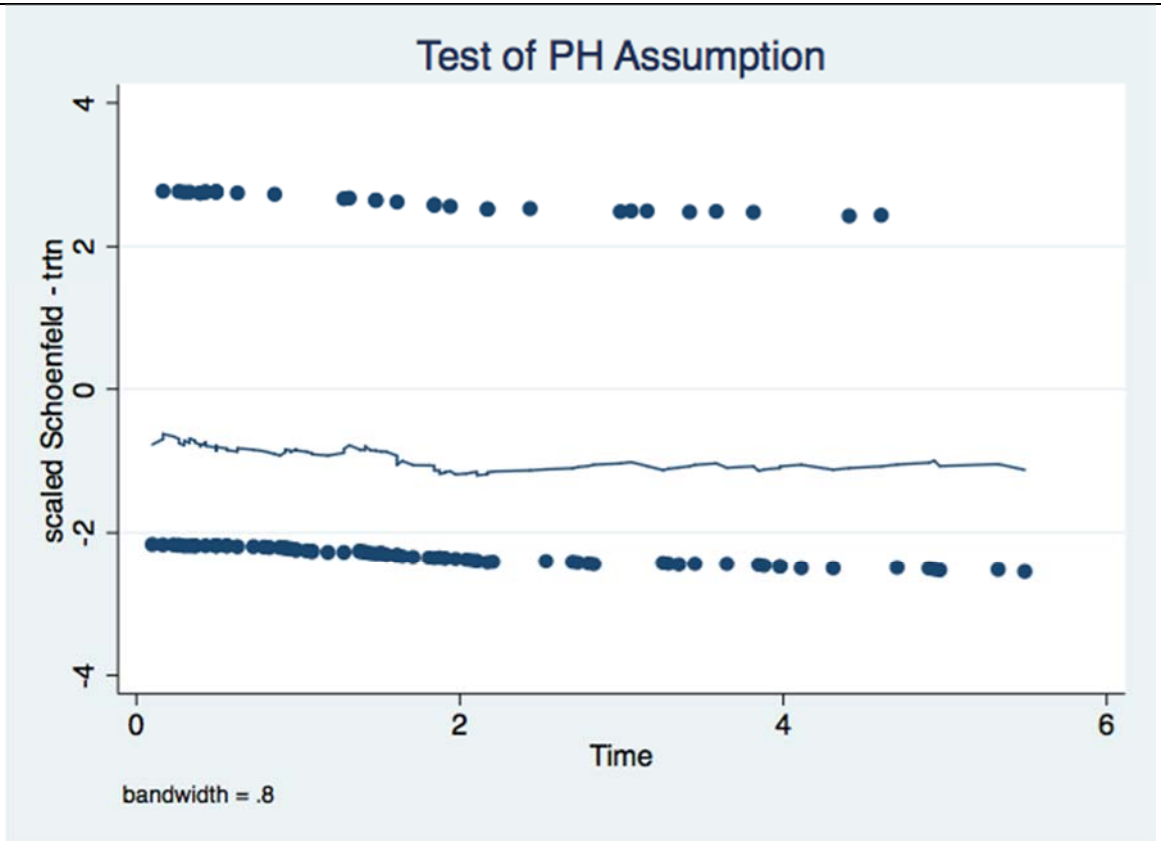


Subgroup	Rifaximin (N=140)	Placebo (N=159)	P Value for Treatment Effect
	no. of patients		
Region			
United States and Canada	101	118	<0.001
Russia	39	41	0.03
Sex			
Male	75	107	0.009
Female	65	52	<0.001
Age			
<65 yr	113	128	<0.001
≥65 yr	27	31	0.01
Race or ethnic group			
White	118	139	<0.001
Other	22	20	0.046
MELD score			
≤10	34	48	0.01
11–18	94	96	<0.001
19–24	12	14	0.21
Conn score			
0	93	107	0.002
1	47	52	0.003
Lactulose use at baseline			
Yes	128	145	<0.001
No	12	14	0.33
Diabetes			
Yes	44	56	0.01
No	96	103	<0.001
Duration of remission			
≤90 Days	100	110	<0.001
>90 Days	39	48	0.04
No. of HE episodes in previous 6 mo			
2	97	111	0.002
>2	43	47	0.003
TIPS			
Yes	12	20	0.03
No	128	139	<0.001
Time to first breakthrough HE episode	140	159	<0.001

Figure 3. Results of the Subgroup Analysis.

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

7.	Section 3.26	The ERG stated that a 5-year time horizon was appropriate in the manufacturer's original model to capture the relevant costs and benefits, but stated that in the revised analysis a lifetime time horizon would have been appropriate given that approximately 52% of patients in the rifaximin-α arm and 45% of patients in the placebo arm were alive after 5 years.	A revision of the time horizon has been carried out in line with the committee's request. The last patient within the economic model dies at 42 years. This is Norgine's definition of life time horizon. Please see section 3 of Norgine Response to NICE TAC's Request for Further Analysis on Rifaximin-α 550mg.
8.	Section 3.27 Page 21	The ERG reviewed the manufacturer's updated analysis and stated that it was unclear why the manufacturer used different time points to censor survival times when modelling breakthrough overt hepatic encephalopathy episodes; data censoring took place at day 168 in the manufacturer's original analysis and at day 170 in the updated analysis.	The schedule of assessments for RFHE3001 defines End of study (EoS) as 168 days ±2 days. Therefore, the revised presentation of regression coefficients based on 170 days censoring is more consistent with the design of the pivotal efficacy study (Bass et al). The treatment effect for rifaximin-α 550mg is identical whether 168 or 170 days are used.
9.	Section 3.27 Page 21-22	The ERG stated that the manufacturer should have carried out some validity tests to assess the assumption of a proportional treatment effect between rifaximin-α and placebo when fitting the parametric distributions to the trial data.	In order to test the proportional hazards assumption over the 6 month observation period of RFHE3001. A Cox proportional survival model was created so as to test the Pearson correlation between Schoenfeld residuals and the rank of survival time for cases that progressed to an event. The result of this analysis was also plotted in graphical form as shown. There was no significant correlation between treatment allocation and Schoenfeld residuals (p=0.1865); an observation supported by the horizontal plot of the same data. Therefore, no evidence was found for a violation of the proportional hazards assumption for treatment effect.



Time: Rank(t)

	rho	chi2	df	Prob>chi2
trtn	-0.12372	1.75	1	0.1865
global test		1.75	1	0.1865

Examination of the subgroup analysis in the RFHE3001 provides evidence that the treatment effect is durable. Figure 3 shows that for subgroups defined by number of prior HE episodes (2 vs. >2 [max 9]) the HR for rifaximin is identical and highly statistically significant (p=0.002 and p=0.003 respectively). A near-identical pattern is also observed for subgroups defined by duration in covert

			/ minimal HE state (*'remission'*) (≤90 days vs. >90 days).
10.	Section 3.28 Page 22	However, it was concerned that combining all subsequent episodes into 1 health state does not take into account the number of episodes and does not fully address the issues around the complexity of disease progression.	Norgine recognises that a more detailed model would have been desirable to fully capture the complexity of disease progression. However, NICE's technical team had made it clear to Norgine that presentation of a new model structure would be unacceptable within the context of additional analysis (Addendum). Therefore, all revisions and supporting data have been presented consistent with the original model structure.
11.	Section 3.28 Page 22	However, it stated that the manufacturer should have taken further steps to assess the goodness of fit of the distributions used and that the gamma distribution should have been included for completeness.	Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) have been calculated as suggested. The rank order of the candidate distributions presented in the Addendum is unchanged. An alternative parameterisation method for the Gompertz distribution consistent with the statistical application used to generate the parameter estimates (Stata) was ranked higher than the original Gompertz model (R) goodness of fit estimation presented in the Addendum.

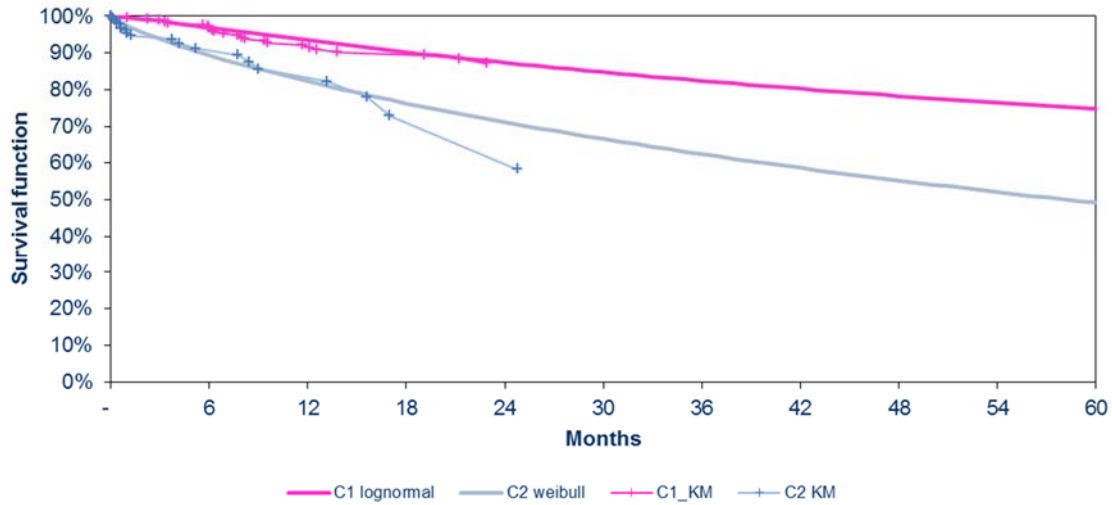
RFHE3001 C_1 to O_1 transition

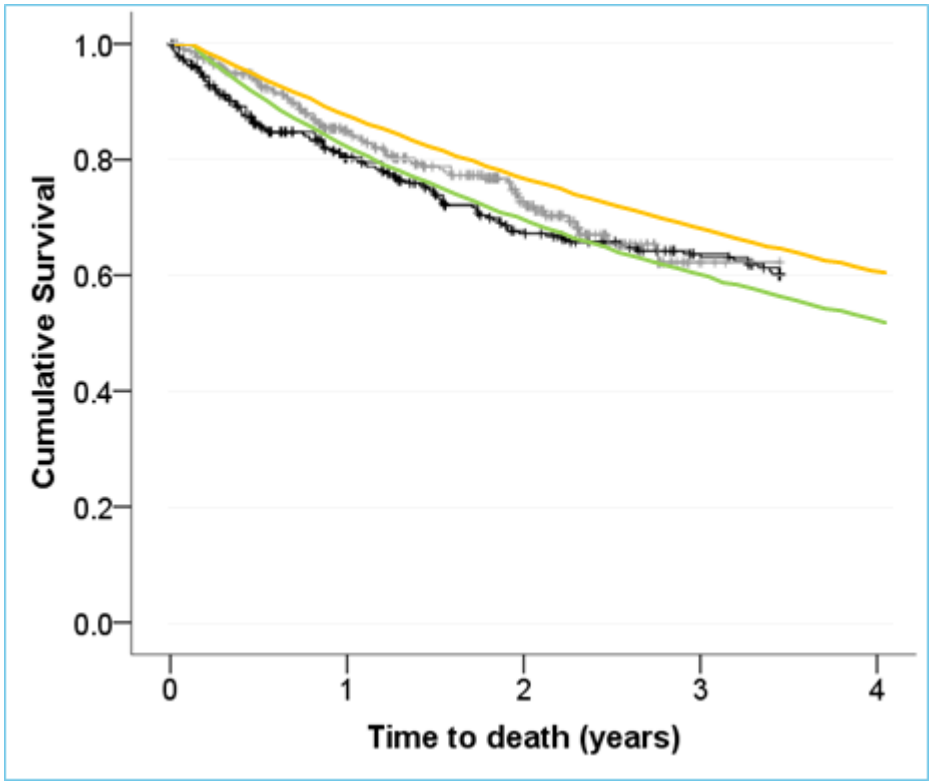
Model	Obs	ll(model)	AIC	BIC
lognormal	299	-748.68	1499.36	1503.09
"cure" gompertz	299	-749.02	1500.05	1503.78
loglogistic	299	-752.93	1507.87	1511.60
weibull	299	-755.58	1513.16	1516.89
exponential	299	-758.56	1519.11	1522.84
"original" gompertz	299	-758.56	1519.11	1522.84

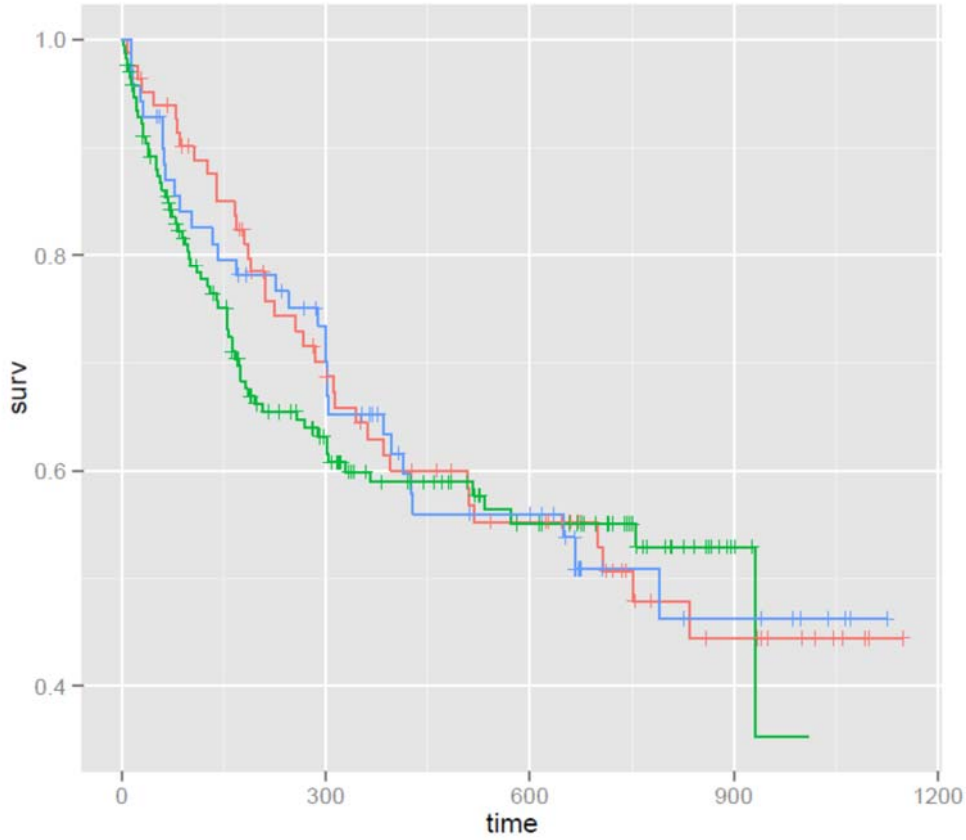
RFHE3002new C_2 to O_2 transition

Model	Obs	ll(model)	AIC	BIC
lognormal	102	-377.20	754.40	754.40
"cure" gompertz	102	-377.56	755.11	755.11
loglogistic	102	-377.80	755.60	755.60
weibull	102	-381.78	763.57	763.57
exponential	102	-388.57	777.14	777.14
"original" gompertz	102	-388.57	777.14	777.14

- Choice of distribution curve fitting the covert to first-observed BOHE (C_1 to O_1) has little impact on ICER (range £18,946 [weibull] to £20,829 [lognormal]).

			• Time constraints prevented exploration of all possible parametric modelling options. We do not believe the gamma distribution would significantly affect the ICER.
12.	Section 3.29 Page 23	The ERG stated that the manufacturer did not justify using different approaches to model mortality, that is, using survival analysis to model mortality in the remission states and using simple proportions to estimate the probability of death in the overt states. It also stated that the manufacturer did not also explain how it calculated the probability of death in the overt states.	The Addendum submitted by Norgine clearly states the methods used to calculate overt mortality (Addendum Sections 4.3.4.2 and 4.3.4.3, page 37) A simple proportion was calculated to estimate probability of death in overt state (O_1 & O_2) rather than survival analysis because the model fixes time in these states at 30.4 days. It is not reasonable to model survival over a period of one model cycle. Patients who did not die in these states were assumed to recover to a subsequent covert state (C_2). Probability of death in the overt state (O_1 and O_2 [all subsequent episodes pooled] respectively in RFHE3002) was calculated as: number of deaths within 31 days of HE onset/number of episodes. Standard errors of the probabilities have subsequently been calculated and applied in the PSA
13.	Section 3.29 Page 23	It noted that the Kaplan-Meier curves were not provided for visual comparison of the different distributions used to model mortality in the remission state and stated that the manufacturer should have taken further steps to assess the goodness of fit of the distributions used to extrapolate mortality.	See Figure 7 below (from section 2.1.2 of Norgine Response to NICE TAC's Request for Further Analysis on Rifaximin-α 550mg).  **Figure 7. Fitted survival functions from RFHE3002 covert (C1) and subsequent covert (C2) states.**
14.	Section 3.29 Page 23	The ERG also highlighted the inconsistency in the use of RFHE3002 data in the model, in which data for all patients in RFHE3002 were used to	The reason for use of different subsets for different inputs was clearly explained in the Addendum. (Addendum Sections 2.2.3 [Subsequent BOHE Episodes] and 4.3.2 [Mortality]) Whilst there were sufficient subsequent HE episodes in RFHE3002 new patients to calculate

		model mortality, whereas only data for new patients in RFHE3002 were included in the modelling of subsequent episodes.	parametric survival models, there were insufficient deaths in this subgroup to inform survival modelling. Covert mortality: new patients, 11 deaths; rollover patients, 6 deaths; crossover patients, 6 deaths. Subsequent covert mortality: new patients, 8 deaths; rollover patients, 4 deaths; crossover patients, 7 deaths. The overall modelled mortality is a very close fit to clinically observed mortality in patients surviving a median of 11 months following first-ever HE  Key to figure: grey line, CPRD HE patients from 11 months after 1st HE code, censored by liver transplant; black line, 3002 mortality, all patients ; green line, modelled lactulose; yellow line, modelled rifaximin. Please see Figure 3 of the Addendum – no statistically significant difference between cross-overs,

			roll-overs and new patients in transition to first observed HE. Therefore modelling covert mortality with combined RFHE3002 data was justified.  **Figure 1. Unadjusted KM plots of time to first BOHE event stratified by OLT subgroup (red, 3001 placebo crossover; green, 3002 new; blue, 3001 rifaximin rollover)**
15.	3.30	The ERG compared mortality from RFHE3001, RFHE3002, the CPRD data and the revised model. It noted that the model over-estimated mortality for the placebo arm at 6 months (10%) compared with RFHE3001 (7%), whereas mortality estimated for the	One would not expect to see differences in mortality at 6 months as this was not a specified end point of RFHE3001. In addition, the study was not powered to detect mortality differences over such a short time period. Norgine has further explored the data relating to mortality in this patient population and presented a sensitivity analysis as requested by the Committee (Please see Section 2 of Norgine Response to Committee's Requests), which illustrates that the cost-effectiveness of rifaximin-α is

		rifaximin-α arm at 6 months was similar to that in RFHE3001 (7%)	no longer primarily driven by mortality.
16.	3.30	The ERG stated that clinical opinion indicated that, although the survival benefit predicted was reasonable, the overall mortality seemed low for patients in both arms of the model It also noted that 2-year mortality for the rifaximin-α arm was similar to that observed in RFHE3002 and that 5-year mortality estimated from the model showed an incremental survival benefit of 8% for rifaximin-α compared with placebo	Modelled mortality is lower than typically seen when measured from first HE episode (e.g. Bustamante, CPRD analysis) precisely because the modelled population is that recruited to the RFHE3001 and RFHE3002 studies whose median time from first HE episode was 11 months, placing them at a much lower hazard of death than would be expected from first HE episode. The comparison of observed overall mortality from RFHE3002 with that of CPRD patients left censored at 11months (median time from first HE to recruitment into the OLE study), as illustrate in the previous figure shows that the former is representative of UK clinical practice and therefore an appropriate data source for modelling mortality in this patient population.
17.	Section 3.30 Page 23	… and also that a higher number of liver transplants would be expected among people with hepatic encephalopathy (only 1 liver transplant was reported in RFHE3001).	It is not unexpected that only 1 liver transplant was reported in the pivotal study since the following was an exclusion criterion for the study *'Subject was expected to receive a liver transplant within 1 month of screening'*.
18.	Section 3.31 Page 24	However, it stated that clinical opinion did not support the use of an aggregated probability for the rifaximin-α and placebo arms, even though the manufacturer showed that the differences between the individual probabilities were not statistically significant. The ERG stated that the more conservative approach of using the individual probabilities should have been taken and, when this was explored in a scenario analysis, the ICER increased slightly to £21,389 per QALY gained	This makes minimal difference to the ICER. Norgine's base case with a life time horizon used an aggregate probability of HE hospitalisation of 52.88% for which the ICER was £17,826/QALY. For a sensitivity analysis where probability HE hospitalisation was split by observed data for treatment arms in RFHE3001 61.3% vs.49.3%, the ICER was £18,130/QALY.
19.	Section 3.32	The ERG stated that it was unclear why	In Norgine's view deriving Utility from the time weighted average CLDQ is the most appropriate

	Page 24	the manufacturer used the EQ-5D utility values estimated from the condition-specific CLDQ in the model given that it was possible to incorporate values directly from mapping the SF-36 utilities onto the EQ-5D.	methodology and thus should form the base case for cost-effectiveness analysis for the following reasons: 1. Domains of SF-36 have a much wider variance than CLDQ domains (CSR RFHE3001) suggesting it is a less precise instrument for measuring QoL in this patient population with underlying cognitive 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 (CSR RFHE3001) 3. SF-36 was an optional instrument in the scheduled assessments whereas CLDQ was a required assessment (in USA and Canada). 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 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[3] (NICE DSU Technical Support Document 10). 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. **Reference:**

			1. Salix Pharmaceuticals Inc. Clinical Study Report. A Multi-Center , Randomized , Double-Blind , Placebo Controlled Trial to Evaluate the Efficacy , Safety and Tolerability of Rifaximin 550 mg BID for 6 Months in Preventing Hepatic Encephalopathy (RFHE3001). Morrisville, NC, 2009. 2. Sanyal A, Younossi ZM, Bass NM, *et al.* Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy - a double-blind placebo-controlled study. *Alimentary Pharmacology & Therapeutics* 2011; **34**: 853–61. 3. Longworth, L., Rowen, D. NICE DSU Technical Support Document 10: The use of mapping methods to estimate health state utility values. 2011. Available from http://www.nicedsu.org.uk 4. Riemsma RP, Forbes CA, Glanville JM, Eastwood AJ, Kleijnen J. General health status measures for people with cognitive impairment: learning disability and acquired brain injury. Health Technol Assess 2001;5(6).
20.	Section 3.32 Page 24-25	It was concerned that the estimated quality-of-life increment with rifaximin-α compared with placebo in the remission state was in contrast to the manufacturer's original analysis in which the impact on quality of life was linked to movement between the overt and remission health states only.	In the first ACD, the Committee questioned why Norgine had not used the QoL data collected during the RFHE3001 study in the original submission. In response to this, Norgine re-examined these data in detail using the methodology described elsewhere and noted significant changes in time-weighted utility between the rifaximin and placebo arms for patients in the covert state and applied this in the model.
21.	Section 3.32 Page 25	The ERG stated that there was uncertainty in the validity of the utility increment estimated for the rifaximin-α arm given that the manufacturer appeared to have measured the value in centimetres directly from the study by Sanyal et.al rather than using the actual published value of difference in least square means.	Norgine did not have access to the original data files of the Sanyal post hoc analysis, nor were the numbers underpinning the Figures published, therefore our only option (within the time available to submit the revised analysis) was to obtain the data by measurement. As digital measurement (using DigitizeIt software) was accurate to 0.1mm we do not believe this introduced any significant uncertainty into the model.
22.	Section 3.32 Page 25	It also highlighted that applying the increment to the remission state only further increased the uncertainty because the incremental value reported in the study represents the CLDQ data	As the data from Sanyal et al only considered those values observed in the covert state ('*remission*'), Norgine considers that the decision to incorporate the increment into the covert states only was a reasonable one. **Reference**: Sanyal A, Younossi ZM, Bass NM, *et al.* Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy - a double-blind

		collected for the whole duration of treatment in the trial.	placebo-controlled study. *Alimentary Pharmacology & Therapeutics* 2011; **34**: 853–61.
23.	Section 3.32 Page 25	The ERG stated that the utility values used in the model were a key driver of the results given that excluding the utility increment from the rifaximin-α arm of the remission state increased the ICER to £59,421 per QALY gained.	Norgine recognise that utility is a key driver of cost-effectiveness in the model. Clinical opinion unanimously supports a clinically meaningful improvement in quality of life associated with rifaximin-α therapy. Therefore, the scenario modelled by the ERG is not clinically plausible.
24.	Section 3.33 Page 25	However, it noted that the cost of outpatient attendance for non-hospitalised hepatic encephalopathy events used in the updated analysis (£176.27) was different from the cost of £110.68 used in the original analysis	The cost in the original submission was incorrectly specified from the tariff for 'Clinical Haematology' (Service Code 303). This was corrected in the Addendum to the tariff for 'Hepatology' (Service Code 306).
25.	Section 4.2 Page 27	The Committee noted that patients with more severe liver disease (Model End Stage Liver Disease [MELD] score of 25 or more) were excluded from the trial, but that the manufacturer had suggested that the trial results may apply to this group. It noted the Evidence Review Group's (ERG) concerns that this was unlikely because the effectiveness of rifaximin-α in the subgroup of patients with MELD scores of 19 to 24 was not statistically significantly better than placebo, although the Committee recognised that this subgroup comprised only 26 of the 299 patients in RFHE3001. However, the Committee heard from the clinical specialists that, in practice, patients with a MELD score greater than 24 have a poor prognosis and are often hospitalised awaiting liver transplant.	Norgine would like to clarify that non significance was due to small 'n' numbers of patients (26 out of 299). The data did, however, show a trend towards significance. (text from Norgine's Response to the 1st ACD) For clarity, patients with MELD score ≥25 were excluded from RFHE3001 for a number of reasons, including the ethical and practical constraints of assessing and studying patients with severe liver disease who are often close to the end of their life. Extensive consultation with clinical experts revealed that patients with MELD Score >19 are treated with rifaximin-α in clinical practice. However, the treatment goals are focused on improvement in QoL / optimisation of the patients clinical condition to make them candidates for liver transplantation. The concern of the ERG is not substantiated by the evidence. Figure 3 of the Bass study clearly indicates that the mean effect favouring rifaximin in subgroup with the highest MELD scores is well within the confidence limits of the two more populous subgroup with lower MELD scores. That it does not achieve statistical significance, is entirely to be expected from the very small numbers of patients available. The Hassest study, whilst being descriptive does provide evidence of effect in patients with a high MELD score.

		The clinical specialists stated that rifaximin-α would not generally be prescribed for these patients because it was unlikely to provide any meaningful benefit.	
26.	Section 4.3 Page 28 (Also Summary of Appraisal Committee's key conclusions) Page 40 - 45	However, the improvements in asterixis score and venous ammonia levels were not statistically significant, and the difference in changes in CLDQ fatigue scores, SF-36 scores and Epworth Sleepiness scale scores between the rifaximin-α arm and placebo arm was minimal.	To clarify, these were tertiary endpoints (ESS and SF-36) for which the trial was never powered. Also, patients who had an episode of BOHE exited the trial (RFHE3001) as per the study protocol. Therefore, patients for whom QoL data were available at end of study were all in the covert (minimal HE) state as they were at the beginning of the study. Consequently, it cannot be expected (a priori) that statistically significant unadjusted differences in QoL would be detectable between baseline and last measurement. It is important to note that, because of altered mental and neuromotor status, it was not possible for subjects to complete the CLDQ, SF-36 and other QoL assessments during an overt HE breakthrough episode. Thus some CLDQ assessments must have occurred as patients were entering an overt episode (which would only have been evident after diagnosis of the episode). Therefore, as mental status was closer to baseline levels at the time of end of treatment assessments, QoL results may have been similar to baseline levels for subjects who had breakthrough overt HE episodes. The planned statistical analysis did not take into account that patients at the end of the study would be those who never experienced a BOHE and was flawed in that respect. Post hoc analysis of CLDQ data (Sanyal et al 2011) showed significant improvement for rifaximin over placebo in all domains of disease-specific QoL and in 27 of 29 individual item responses. As we have previously stated, QoL is extremely difficult to measure in these patients. For the following reasons: 1. Cognitive impairment whereas patients believe they are perfectly normal 2. Generic measures e.g. SF-36 3. Time weighted averages are the most useful way of capturing Please also see Response to: • ACD Section 3.32; regarding CLDQ and SF-36 scores • ACD Section 3.6 **Reference:** Sanyal A, Younossi ZM, Bass NM, et al. Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy - a double-blind

			placebo-controlled study. Alimentary Pharmacology & Therapeutics 2011; 34: 853–61.
27.	Section 4.5 Page 30	The Committee considered the manufacturer's economic model and the ERG's critique of the model. It accepted the exclusion of neomycin from the analysis because it was not routinely used in clinical practice. The Committee noted that after consultation, the manufacturer amended the way it estimated the risk of subsequent episodes and that the revised model assumed that the risk of subsequent hepatic encephalopathy episodes depended on time since the first episode. The Committee was aware that all subsequent episodes were combined in 1 health state, that is, subsequent remission state and subsequent overt state; thereby ignoring the number of episodes. However, it noted that including more health states for subsequent episodes would increase the complexity of the model and would be difficult to populate with the current evidence base. The Committee therefore concluded that, although the number of episodes was not considered, the revised model was an improvement on that used in the manufacturer's original analysis, which oversimplified the nature and course of the disease.	As stated above, whilst Norgine recognises that a more detailed model would have been desirable to fully capture the complexity of disease progression, due to the constraints of what type of analysis would be accepted as additional analysis it was not possible to fully explore separating out subsequent BOHEs, whilst remaining consistent with the original model structure. (See Norgine Response to ACD Section 3.28 …page 22)
28.	Section 4.6 Page 31	It noted that the ERG had conducted an exploratory analysis with a lifetime time	It is unclear how the ERG conducted their exploratory analysis of a 35 year life time horizon. Also, this is in contradiction to ACD Section 3.26 which states the ERG used a life time horizon of 40yrs.

		horizon where all patients died after 35 years. However, it heard from the clinical specialist that people with hepatic encephalopathy would not survive for up to 35 years because of their underlying liver cirrhosis. The clinical specialist stated that life expectancy usually ranged between 5 and 15 years depending on disease severity, stating that it was even lower for people with severe disease who had not had a liver transplant. The Committee noted that a time horizon of 35 years did not imply that all patients survived for 35 years. It considered that the prolonged survival of 35 years in the model could be a result of extrapolating outcomes using the log normal distribution, which has a long tail and could lead to implausible survival results. The Committee concluded that the manufacturer's choice of a 5-year time horizon was not in line with the NICE reference case and that a lifetime time horizon would be more appropriate to capture all relevant costs and benefits. It recommended that further analyses using a lifetime time horizon be requested.	Norgine has carried out further analysis using a life time horizon, as per the committee's request and this resulted in a 42 year time horizon by which time the last patient within the economic model is dead. Please see section 3 of Norgine Response to NICE TAC's Request for Further Analysis on Rifaximin-α 550mg
29.	Section 4.8 Page 33	First, the Committee was unsure why the manufacturer had not presented results based on mapping SF-36 data collected from RFHE3001 directly to EQ-5D. The Committee considered that	The high variance in SF-36 scores compared to CLDQ scores indicates that SF-36 is insufficiently sensitive to capture the QoL benefits of rifaximin treatment. In Norgine's view deriving Utility from the time weighted average CLDQ is the most appropriate methodology and thus should form the base case for cost-effectiveness analysis for the following

		incorporating further modelling steps after the mapping exercise to quantify the relationship with CLDQ scores unnecessarily introduced further uncertainties in the analysis.	reasons: 1. Domains of SF-36 have a much wider variance than CLDQ domains (CSR RFHE3001) suggesting it is a less precise instrument for measuring QoL in this patient population with underlying cognitive 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 (CSR RFHE3001) 3. SF-36 was an optional instrument in the scheduled assessments whereas CLDQ was a required assessment (in USA and Canada). 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 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[3] (NICE DSU Technical Support Document 10). 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. **Reference:** 1. Salix Pharmaceuticals Inc. Clinical Study Report. A Multi-Center , Randomized , Double-

			Blind , Placebo Controlled Trial to Evaluate the Efficacy , Safety and Tolerability of Rifaximin 550 mg BID for 6 Months in Preventing Hepatic Encephalopathy (RFHE3001). Morrisville, NC, 2009. 2. Sanyal A, Younossi ZM, Bass NM, *et al.* Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy - a double-blind placebo-controlled study. *Alimentary Pharmacology & Therapeutics* 2011; **34**: 853–61. 3. Longworth, L., Rowen, D. NICE DSU Technical Support Document 10: The use of mapping methods to estimate health state utility values. 2011. Available from http://www.nicedsu.org.uk Riemsma RP, Forbes CA, Glanville JM, Eastwood AJ, Kleijnen J. General health status measures for people with cognitive impairment: learning disability and acquired brain injury. Health Technol Assess 2001;5(6).
30.	Section 4.9 Page 34	The Committee also expressed concern regarding the face validity of the utilities used in the model. It noted that the difference between the remission and overt state utility values was less than the benefit assumed for rifaximin-α compared with placebo for the remission state.	The intention with the model revisions was to use input assumptions substantiated with available data. Given that a small number of CLDQ observations from RFHE3001 had been made in the overt state, a health state utility was estimated from this. It is important to highlight that as a patient enters an overt episode, their ability to adequately complete a QoL questionnaire becomes progressively impaired to the point where this becomes impossible once the patient has fully entered the overt state. The above CLDQ assessments must, therefore, have occurred as patients were entering an overt episode (which would only have been evident after diagnosis of the episode). For this reason, the assessment would not capture the full disutility associated with the overt HE episode. Thus, the values presented may well be an underestimation and has the effect of making the model conservative.
31.	Section 4.9 Page 35 (Also Summary of Appraisal Committee's key conclusions) Page 40 - 45	Given the concerns around methodology and the inconsistencies identified in the results available, the Committee considered that the utility estimates driving the model were not robust. The Committee concluded that it would be more appropriate to use utility values estimated by mapping SF-36 data from the entire RFHE3001 population directly to EQ-5D and it recommended that further analyses	This analysis has been carried out in line with the committee's request. Please see Section 4 of Norgine Response to Committee's Requests. With respect to uncertainties surrounding use of the CLDQ EQ-5D mapping function, the requested PSA for the Norgine Basecase incorporates the uncertainty of both the LS mean incremental difference in CLDQ Overall score favouring rifaximin-α (Sanyal et al)[1] and that of the parameter estimate relating CLDQ to EQ-5D of the repeated measures modelling. This is line with NICE's recommendation (NICE DSU Technical Support Document 10)[2]. **Reference:** 1. Sanyal A, Younossi ZM, Bass NM, *et al.* Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy - a double-blind

		incorporating this data be requested.	placebo-controlled study. *Alimentary Pharmacology & Therapeutics* 2011; **34**: 853–61. 2. Longworth, L., Rowen, D. NICE DSU Technical Support Document 10: The use of mapping methods to estimate health state utility values. 2011. Available from http://www.nicedsu.org.uk
32.	Section 4.10 Page 35	It also noted that length of stay was assumed to be 5 days in the model, whereas data from Hospital Episode Statistics for encephalopathy admissions suggests mean stays of around 17 days. The clinical specialist stated that an assumption of 5 days was reasonable. The Committee considered it would have been useful for this information to have been collected in the trial so that differences in length of stay could have been appropriately captured in the model.	There is no HE specific ICD or HRG code. All available codes are surrogates as shown below(HES 2012): 1) For ICD-10 G93.4 'Encephalopathy, unspecified' mean LoS = 17 days, median LoS = 8 days 2) For ICD-10 K72.9 'Failure, hepatic' mean LoS = 12.4 days, median LoS = 7 days 3) For ICD-10 K70.4 'Alcoholic hepatic failure' mean LoS = 13.6 days, median LoS = 8 days 4) Weighted averages for HRGs GC01 & GC15, mean LoS = 13.5, median LoS = 8.7 It is worthy of note that the Norgine assumption of 5 days is conservative and based on clinical expert opinion. **Reference:** HES Summary Data 2012
33.	Section 4.11 Page 36	However, the Committee was concerned that the model predicted a difference of 3.6% in the risk of mortality with rifaximin-α compared with placebo during the first 6 months of the model and a difference of up to 8% over the 5-year time horizon. It noted that no differences in mortality between rifaximin-α and placebo were observed in RFHE3001	One would not expect to see differences in mortality at 6 months as this was not a specified end point of RFHE3001. In addition, the study was not powered to detect mortality differences over such a short time period. Norgine has further explored the data relating to mortality in this patient population and presented a sensitivity analysis as requested by the Committee (Please see Section 2 of Norgine Response to Committee's Requests), which illustrates that the cost-effectiveness of rifaximin-α is no longer primarily driven by mortality. Please see response to ACD section 3.30 and 4.11(below)
34.	Section 4.11 Page 37	The Committee was not persuaded that these data provided robust evidence for a differential mortality benefit for rifaximin-α for preventing recurrence of overt hepatic encephalopathy.	The evidence for elevated mortality immediately following HE is well documented [Shawcross et al]. As rifaximin-α is effective in preventing HE episodes the case for an indirect mortality benefit is entirely plausible and supported by clinical experts. Please also see response to ACD Section 4.12 (below) **Reference:** Shawcross DL, Sharifi Y, Canavan JB, et al. Infection and systemic inflammation, not ammonia, are associated with Grade 3/4 hepatic encephalopathy, but not mortality in cirrhosis. Journal of

			hepatology 2011; 54: 640–9.
35.	Section 4.12 Page 37	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 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 and overt states derive from the reduction in episodes of overt HE provided by rifaximin-α treatment. In the covert state, 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. 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 plausible as such an event marks a deterioration in underlying liver disease status and will have had 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 [1]. In the overt state mortality risk was calculated from the 30-day mortality following O_1 and O_2 events, 11% and 8% respectively. This acute elevation in the risk of death following breakthrough overt HE is well established (Bustamante et al., 1999; Shawcross et al., 2011). 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:
36.	Section 4.12 Page 38	'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	1) avoidance of the acute 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-α are clinically plausible. In the model, prior to the first HE episode, both cohorts have the same risk of dying, the rate derived from the log normal distribution derived from RFHE3002. During the first overt HE episode both cohorts have an 11% risk of death. In patients who survive the first and subsequent episodes the mortality risk for both cohorts is derived from the Weibull distribution obtained from RFHE3002. The mortality risk during the second and any further overt episodes is 8% for both cohorts. Norgine sought additional clarification from NICE's Technical Team on how to address the committee's request on '*a clinically plausible diminishing mortality benefit with rifaximin-α over*

		both health states'.	*time'* 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 (Section 2.1.2) of Norgine Response to Committee's Requests. 1. Bajaj JS, Schubert CM, Heuman DM, et al. Persistence of cognitive impairment after resolution of overt hepatic encephalopathy. Gastroenterology. 2010;138:2332-2340. 2. Bustamante, J., Rimola, a, Ventura, P. J., Navasa, M., Cirera, I., Reggiardo, V., & Rodés, J. (1999). Prognostic significance of hepatic encephalopathy in patients with cirrhosis. Journal of hepatology, 30(5), 890–5. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20508990 3. Shawcross, D. L., Sharifi, Y., Canavan, J. B., Yeoman, A. D., Abeles, R. D., Taylor, N. J., … Wendon, J. A. (2011). Infection and systemic inflammation, not ammonia, are associated with Grade 3/4 hepatic encephalopathy, but not mortality in cirrhosis. Journal of hepatology, 54(4), 640–9. doi:10.1016/j.jhep.2010.07.045
37.	Section 4.13 Page 39	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."	
38.	Section 4.13 Page 39	The Committee was also concerned that the manufacturer did not report a probabilistic ICER that would take account of all the uncertainties in the model parameters simultaneously.	The probabilistic Sensitivity Analysis has been carried out as per the committee's request with the following results: Probabilistic ICER: £29,551/QALY; probability of cost-effectiveness at WTP £30K, 42%. Please see Section 4 of Norgine Response to Committee's Requests.