Addendum to Norgine NICE STA Submission on Rifaximin-α 550mg: Further Analyses in Response to Technology Appraisal Committee's Critique of the Economic Case (AIC Redacted)

Executive Summary

Following the NICE appraisal consultation process in June 2013[1] to assess the use of rifaximin-α 550mg to reduce recurrence of overt episodes of hepatic encephalopathy (HE) in patients with liver cirrhosis, Norgine Pharmaceuticals has undertaken an update to the review of published literature and a new set of data analyses to update and "re-balance" the cost-effectiveness model.

A randomised placebo controlled trial (RCT) of rifaximin-α 550mg[2,3] in patients in remission from HE, demonstrated a reduction in breakthrough overt hepatic encephalopathy (BOHE) episodes and in the rate of hospitalisation. These patients continued to take a standard of care of lactulose at various doses (91% of patients in both arms were on lactulose). RFHE3002, an open label trial[A] (OLT), was undertaken to assess the longer term safety and tolerability of rifaximin-α 550mg[4,5]. These data have been examined to determine the mortality and risk of episodes occurring over time in these patients.

Norgine presented an economic analysis of RFHE3001 and RFHE3002 to NICE and received detailed comments as part of the Technology Appraisal Committee's (the Committee) review. The following report addresses the concerns highlighted by the Committee:

1. **Model structure: number of transition states, probability of subsequent episodes and extrapolation of survival curves** (see ACD[1] Section 4.5)

No structural changes have been made to the revised model but re-examination of the clinical study data for rifaximin-α 550mg has led to a substantially changed set of inputs and outputs for the cost-effectiveness analysis.

2. **Combination of RFHE3001 and RFHE3002 datasets (use of data on rifaximin patients continuing from RCT to OLT)** (See ACD[1] Section 4.6)

The economic case has been substantially revised and now models an extrapolation of the primary efficacy endpoint of RFHE3001. In addition, RFHE3002 has been utilised to provide key input data for mortality and to populate the probabilities of occurrence of subsequent BOHE.

3. **Utilities: "The Committee concluded that it would be more appropriate to incorporate the quality of life data collected from RFHE3001 in the model and any external data should only be used to supplement and validate this"** (See ACD[1] Section 4.7)

Norgine has re-examined the assumptions for utility in the model and undertaken a utility calculation based on the quality of life (QoL) data recorded within the RCT. This has resulted in the

[A] To enter RFHE3002, subjects were required to have successfully participated in a previous HE study (i.e. RFHE3001) with prior enrolment history of ≥ 2 verifiable overt HE events prior to enrolment into RFHE3001 or, if naive to participation in RFHE3001, enrolled with ≥ 1 verifiable episode of HE associated with cirrhosis or portal hypertension equivalent to Conn score ≥ 2 within 12 months of screening. Subjects who did not participate in a previous HE study with rifaximin were eligible if this open-label study was the only rifaximin HE study open for enrolment at an individual research site

incorporation of the findings of Sanyal et al[6] that demonstrated a significant improvement in disease specific QoL in the remission state for patients on rifaximin-α 550mg vs. placebo.

4. **Mortality: The economic analysis was judged to be too reliant on the direct effect on mortality without any apparent differential mortality benefits between the treatment arms in the pivotal trial (RFHE3001)** (See ACD[1] Section 4.9 - 4.12)

Norgine has undertaken a revision of the mortality assumptions presented in the original model. Norgine commissioned an examination of the primary care and linked Hospital Episodes Statistics (HES) databases using the UK Clinical Practice Research Datalink[7] (CPRD). This examined the mortality rates for HE patients in the UK and validated a further analysis of the mortality of the patients in the OLT. These two sources and a review of literature have resulted in a better understanding of the mortality assumptions for the economic model.

5. **Hepatic encephalopathy related hospitalisation** (ACD[1] Section 3.22 & 3.39)

Norgine's original model contained an incorrect assumption for the rates of hospitalisation for patients who experience BOHE. The model had assumed a differential rate between rifaximin-α 550mg and placebo as observed in RFHE3001. Further review of the data demonstrated this to be statistically insignificant and a single constant assumption of the risk of hospitalisation has now been used within the model for both arms.

Conclusion

Following the revision of the economic model in response to the Committee's critique, the incremental cost-effectiveness ratio (ICER) for rifaximin-α 550mg, when used to reduce recurrence of overt HE, was £20,799 per QALY.

This was demonstrated using a 5-year extrapolation of the pivotal efficacy RCT with a log-normal distribution curve for the intention-to-treat (ITT) population in both the rifaximin-α 550mg and placebo arms.

The cost-effectiveness results from the sensitivity analysis do not vary substantially unless assumptions are altered in the second phase of the model related to subsequent overt HE episodes. The revised model is now stable irrespective of the choice of survival distribution of the primary efficacy endpoint. Furthermore, the revised model reflects current clinical understanding of mortality in this patient population and is less reliant on mortality assumptions to provide a reasonable and stable ICER.

The revised analyses demonstrate that rifaximin-α 550mg represents a cost-effective use of NHS resources in the reduction of recurrence of overt episodes of hepatic encephalopathy in adult patients with cirrhosis in England and Wales.

Summary of Key Model Revisions

Factor	Original values	Resubmission values	Justification	Reference
HEALTH STATE TRANSITIONS				
Remission to overt (first observed breakthrough episode)	Parametric survival distributions fitted to combined dataset (RFHE3001 & RFE3002) for rifaximin to extrapolate beyond 6 months. A log-normal distribution was used in the base case (best fit). Placebo arm fitted a log-normal distribution to RFHE3001 data with replacement of shape parameter from the model fitted to the combined rifaximin dataset.	Parametric survival distribution fitted to RFHE3001 dataset only for both arms. Log-normal distribution also best fit. Discrete time-dependent transition probabilities estimated from the instantaneous hazard rates using the formula detailed in Briggs 2006.	Application of combined dataset to rifaximin arm but not placebo thought to be biased by 'enrichment'. Use of RFHE3001 dataset only for both arms strongly recommended by ERG.	ACD[1] 4.6 Briggs[8]
Remission to subsequent breakthrough episodes	Exponential curve fitted to time to 1st BOHE from RFHE3001 study. Hazard ratio (HR) for rifaximin vs. placebo applied to the placebo survivor function to estimate S_t for rifaximin.	Parametric model with log-normal distribution fitted to a pooled dataset of subsequent transitions observed in newly recruited patients to RFHE3002 (excluding open-label extensions from RFHE3001 study). HR for lactulose calculated from RFHE3001 study and fitted as parameter co-efficient assuming constant treatment effect.	Appraisal committee clinical experts challenged the three assumptions of: 1) independence of HE episode from preceding episodes; 2) independence of HE episodes from time spent in remission; and 3) risk of subsequent HE episodes assumed constant over time. Norgine has commissioned time-to-event analysis of subsequent HE episodes in RFHE3002 showing all three original assumptions to be weak.	ACD[1] 3.38
Covert mortality	Parametric survival distributions fitted to digitised KM plot data from Bustamante 1999 to extrapolate the mortality risk to five years. Log-normal distribution selected (best fit). Time dependent transition probabilities were estimated using the formula detailed in Briggs 2006.	Parametric survival model fitted RFHE3002 first remission state until death or censor (BOHE or dropout). Log-normal distribution applied in base case (best fit).	Original model predicted excessive mortality compared to that observed in RFHE3001 study and NICE clinical experts' opinion. RFHE3002 overall mortality found to be representative of other clinical populations.	ACD[1] 4.9 Bustamante 1999[9] Appendix I[10]

Overt mortality	Conn-score (CS) weighted 28-day mortality derived from expert opinion (CS 1,2) and Shawcross 2011 (25%)	Observed 30-day mortality from first observed HE in RFHE3002 (11.0%)	RFHE3002 data used for consistency as overall OLT mortality shown to be similar to clinical practice.	Shawcross[11] CSR RFHE3001[3]
Subsequent covert mortality	See 'Covert mortality'.	Parametric survival model fitted RFHE3002 from all subsequent remission states (assumed to start 30 days after prior HE) until death or censor (BOHE or dropout). Weibull distribution applied in base case (best fit).	RFHE3002 data used for consistency as overall RFHE3002 mortality shown to be similar to clinical practice.	CSR RFHE3002[4]
Subsequent overt mortality	See 'Overt mortality'.	Observed 30-day mortality from all subsequent observed HEs in RFHE3002 (7.7%)	RFHE3002 data used for consistency as overall OLT mortality shown to be similar to clinical practice	CSR RFHE3002[4]
RESOURCE USE				
Overt HE-related hospitalisation	Unadjusted 1-month probabilities applied from RFHE3001: RIF 14.63%; PLB 10.71%	Pooled probability of 52.88% applied to both arms from RFHE3001. Probability of HE requiring hospitalisation assumed constant for first and subsequent events.	No rate adjustment made as time already accounted for in transition. Post hoc analysis of RFHE3001 hospitalisation found no significant different between arms.	CSR RFHE3001[3]
Outpatient attendance	All non-hospitalised Hes assumed to require 1 outpatient attendance. DoH Tariff chosen £110.68, 'Clinical haematology' (Service code 303)	Same assumption but cost updated to £176.27, 'Hepatology' (Service code 306).	Cost incorrectly specified in previous submission.	DoH NHS reference costs[12].
HEALTH EFFECTS				
Covert utility	Conn-score (CS 0, 1) weighted utility based on Norgine - sponsored TTO study and CS proportions for ITT of RFHE3001 whilst in remission state	SF12-estimated EQ-5D utility mapped to CLDQ scores at baseline; incremental time-weighted average improvement for rifaximin applied from Sanyal 2011 from Month 2 onwards)	ACD not satisfied that the TTO utilities used originally were representative of those observed in clinically similar populations and recommended analysis of QoL data from RFHE3001 to synthesise health utility.	ACD[1] 4.7 Sanyal 2011[6]
Overt utility	Conn-score (CS 1, 2, 3, 4) weighted utility based on Norgine - sponsored TTO study and CS proportions from RFHE3001 whilst in breakthrough overt state	SF12-estimated EQ-5D utility mapped to CLDQ scores observed after BOHE in RFHE3001		

Contents

This report outlines the revisions to the economic model from the original submission to NICE in Feb 2013 in the following sections:

1 Description of Model Structure 7

1.1 Technology Appraisal Committee's Critique of the Model 7

1.1.1 Revised Model Summary 7

1.1.2 Model Description Detail 8

2 Revised Data Inputs for Extrapolation of Both Phases of the Model 9

2.1 Combination of RFHE3001 and RFHE3002 Datasets 9

2.1.1 Executive Summary 9

2.1.2 Methods Overview 9

2.1.3 Study Population 10

2.1.4 Methods (Including Statistical Methods) 10

2.1.5 Analysis 10

2.1.6 Key Results 15

2.1.7 Discussion 15

2.1.8 Summary of Key Findings 15

2.2 First and Subsequent Transitions from Covert to Overt HE States 16

2.2.1 Executive Summary 16

2.2.2 Methods Overview 16

2.2.3 Study Population 17

2.2.4 Methods (Including Statistical Methods) 17

2.2.5 Analysis 18

2.2.6 Key Results 23

2.2.7 Discussion 25

2.2.8 Key Findings 25

3 Use of Utilities in the Cost-effectiveness Model 26

3.1 Executive Summary 26

3.1.1 Methods Overview 26

3.1.2 Study Population 26

3.1.3 Methods (Including Statistical Methods) 27

3.1.4 Analysis 28

3.1.5 Key Results 30

3.1.6 Discussion 30

3.2 Key Findings 31

4 Mortality 32
4.1 Executive Summary 32
4.2 Methods Summary 32
4.2.1 Review of Published Studies and Commissioned Analysis of CPRD Data 32
4.2.2 Summary of Mortality Literature Review & CPRD Analysis Findings 35
4.3 Incorporating Mortality from RFHE3002 into the Revised Economic Model 36
4.3.1 Executive Summary 36
4.3.2 RFHE3002 Study Population 36
4.3.3 Methods (Including Statistical Methods) 36
4.3.4 Analysis 36
4.3.5 Key results 39
4.3.6 Discussion 40
4.3.7 Discussion 41
4.3.8 Key Findings 41
5 Hepatic Encephalopathy-related Hospital Admissions 42
5.1 Executive Summary 42
5.1.1 Methods Overview 42
5.1.2 Study Population 43
5.1.3 Methods (Including Statistical Methods) 43
5.1.4 Analysis 43
5.1.5 Results Summary 44
5.1.6 Discussion 44
5.2 Key Findings 44
6 Economic Modelling Results 45
6.1 Base-case 45
6.2 Sensitivity Analysis 45
7 References 49
8 Appendices 51
Appendix I: Mortality Report 51
Appendix II: CPRD Report 51
Appendix III: Updated Literature Searches 51
Appendix IV: Updated Budget Impact Model 51

1 Description of Model Structure

1.1 Technology Appraisal Committee's Critique of the Model

In the original submission, the cost-effectiveness model presented was described with a simple diagrammatical representation, shown in Figure 1.

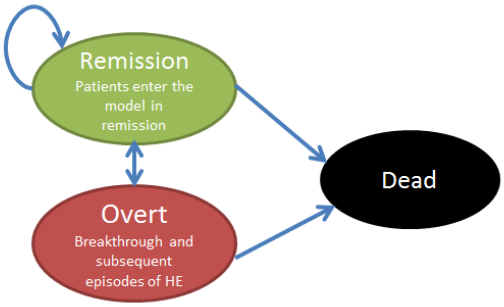


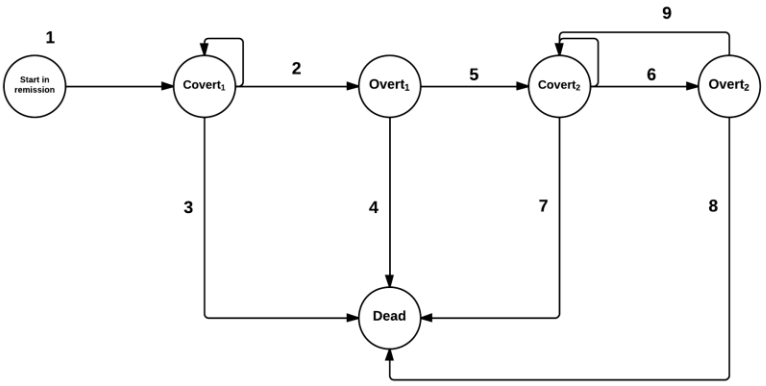
Figure 1. Original representation of rifaximin 550mg cost-effectiveness model

This model assumed that the risk of having subsequent breakthrough overt episodes of hepatic encephalopathy (BOHE) was independent of the risk of preceding episodes and the time spent in the remission state. The Committee expressed concern about the plausibility of this assumption. Furthermore, clinical specialists believe that a previous HE episode increases the likelihood of subsequent episodes and that the risk of mortality would be higher with each additional episode.

The Committee considered that more health states should have been included in the model to capture the complexities around the recurrence of subsequent hepatic encephalopathy episodes and concluded that the model structure oversimplified the nature and course of the disease (ACD[1] Section 4.5).

1.1.1 Revised Model Summary

It is important to note that no structural changes have been made to the model. The revision exercise undertaken by Norgine has focused on updating the model with the most appropriate data based on the feedback from the Committee. The structure of the revised Norgine cost-effectiveness model for rifaximin-α 550mg was designed to reflect the clinical pathway of HE. It is an Excel workbook-based Markov cohort model that broadly consists of 5 states: two remission states – ($Covert_1$ and $Covert_2$), two overt states – ($Overt_1$ and $Overt_2$) and Dead. Figure 1 was judged not to have fully explained this two-phase model approach, thus a more detailed representation is given in Figure 2 below. Norgine believe that a better description and the use of more appropriate data and assumptions will address the concerns of the Committee.



Original model notes

1. Patients enter the model in the remission state
2. $Covert_1$ to $Overt_1$
Log-normal PH survival model fitted from combined 3001+3002 data (assuming constant treatment effect)
3. $Covert_1$ to Death
Log-normal PH survival model fitted to Bustamante 1999 data (+/- all-cause mortality; no treatment effect)
4. $Overt_1$ to Death
30-day mortality applied from expert opinion (Conn score 1&2) plus Shawcross 2011 (CS 3&4) weighted by 3001 BOHE CS (no treatment effect)
5. $Overt_1$ to $Covert_2$
All survivors of $Overt_1$ assumed to return to a subsequent Covert state after 30 days
6. $Covert_2$ to $Overt_2$
Exponential PH survival model fitted to 3001 data (assuming constant treatment effect)
7. $Covert_2$ to Death
Log-normal PH survival model fitted to Bustamante 1999 data (+/- all-cause mortality; no treatment effect)
8. $Overt_2$ to Death
30-day mortality applied from expert opinion (Conn score 1&2) plus Shawcross 2011 (CS 3&4) weighted by 3001 BOHE CS (no treatment effect)
9 $Overt_2$ to $Covert_2$
All survivors of $Overt_2$ assumed to return to a subsequent Covert state after 30 days

Figure 2. Schematic of transitions through the rifaximin-α Markov cohort cost-effectiveness model

1.1.2 Model Description Detail

In order to maintain consistency with the pivotal trial data, patients enter the model in the covert remission state ($Covert_1$) (**1**)[B]. In each monthly cycle, patients can either: remain in remission, progress to the first observed[C] breakthrough overt state (**2**) (which may include hospital admission), or die (**3**) (collectively Phase I). Within the first observed overt state ($Overt_1$), patients have a 30-day probability of mortality (**4**), whereupon survivors progress to the next cycle (**5**) in a subsequent covert remission state ($Covert_2$). No patient returns to the original covert state ($Covert_1$). Similarly, from the subsequent covert state patients can either: remain in remission, progress to the next observed breakthrough overt state (**6**) or die (**7**) (collectively, Phase II). Within the subsequent overt state ($Overt_2$), patients have a 30-day probability of mortality (**8**), whereupon survivors enter the next cycle in a subsequent covert remission state ($Covert_2$) (**9**).

[B] Numbering in this section relates to that illustrated in Figure 2.
[C] Note that this is not the first breakthrough overt HE for any patient as all patients in the model have a history of HE. The same applies throughout this report.

2 Revised Data Inputs for Extrapolation of Both Phases of the Model

Section 2 addresses the issues the Committee raised with regard to how the data and the model interacted to produce its cost-effectiveness results (see ACD[1] Section 4.6). These are:

1. Use of combination of RFHE3001 and RFHE3002 datasets (by way of an "enriched" cohort of RFHE3001 patients) to assist the mathematical extrapolation of the original cost-effectiveness model to 5 years. This has been addressed by adopting a survival distribution for the primary HE episode extrapolated from RFHE3001 data only; in line with the recommendation of the Committee.
2. Use of an exponential survival distribution from RFHE3001 to model transition to subsequent HE events contrary to clinical opinion. This has been addressed by analysis of the RFHE3002 dataset to better understand BOHE and to explore the time to subsequent BOHE to inform an appropriate choice of mathematical extrapolation for the second phase of the economic model.

2.1 Combination of RFHE3001 and RFHE3002 Datasets

2.1.1 Executive Summary

- The previous base-case included modelling time to first BOHE by fitting parametric survival distributions to a dataset that combined RFHE3001 and RFHE3002 rifaximin patients in order to extrapolate the pivotal study results beyond the final 168 days[D] observation point.
- As RFHE3002 included only rifaximin treated patients, data from RFHE3001 only were used for the placebo group. The Committee considered this combination of datasets as inappropriate because it broke randomisation and introduced bias[1].
- Norgine has therefore undertaken a re-factoring of the model to produce a base-case which models the primary efficacy endpoint (time to first BOHE – transition [2] in Figure 2), using only the RFHE3001 data.
- It is important to note that the RFHE3002 study reports event data considerably beyond the 6-month horizon of RFHE3001 to which more reliable extrapolations to the base-case 5-year economic model horizon can be made.
- A series of analyses found no meaningful differences in time to first observed BOHE between either: RFHE3002 strata[E] or RFHE3001 rifaximin-treated patients and new rifaximin-naïve RFHE3002 patients. These findings suggest that RFHE3002 would be a representative dataset from which to model subsequent BOHE events and mortality.

2.1.2 Methods Overview

A key concern of the Committee regarding Norgine's initial submission was the use of the RFHE3002 (OLT) data in the modelling of first observed BOHE. Study RFHE3001 was a randomized controlled trial (RCT) which recorded time to first observed BOHE events only; whereas RFHE3002 recorded first and subsequent BOHE over a longer period of time (with at least 24 months planned rifaximin treatment per subject at enrolment).

The RCT comprised of a rifaximin treatment arm and a placebo arm; whereas all subjects in the OLT were treated with rifaximin. Three distinct patient subgroups were created by enrolment:

[D] The end of study assessment was scheduled for 168±2 days.
[E] RFHE3002 strata: 1) Rifaximin naïve 'new' patients; 2) patients continuing rifaximin, 3) patients crossing over from placebo treatment.

1. those ‘rolling over’ from the rifaximin arm of RFHE3001 (roll-over),
2. those ‘crossing over’ from the placebo arm of RFHE3001 (crossover),
3. rifaximin naïve subjects, who were not recruited into RFHE3001, but newly recruited into RFHE3002 (new).

One of the concerns expressed by the Committee was that only data on roll-over subjects in the OLT were used in the combined modelling, constituting a possible enrichment of the data. This concern was substantiated by the observation that the ICER in the original model base-case was sensitive to the distributional form of the covert to overt transition models based on combined RFHE3001 and RFHE3002 data.

As the RFHE3002 study was designed to reflect the natural history of recurrent HE, it is a useful source of addressing the limitations of the original economic model, particularly, the modelling of subsequent covert to overt HE transitions and mortality.

The objective of this section is to explore the differences or similarities between the rifaximin arm of the RFHE3001 study and the three rifaximin treated subgroups of the RFHE3002 study, in order to justify the development of survival models (for BOHE and death) from the OLT in preference to extrapolation beyond the 6-month horizon of the RFHE3001 RCT.

2.1.3 Study Population

In this analysis the study population was all patients enrolled into RFHE3002, with emphasis on the source of enrolment as subgroup analysis. For subjects also enrolled (and having ‘survived’ event-free) to the RFHE3001 RCT, analyses were repeated by combining their data from both studies.

2.1.4 Methods (Including Statistical Methods)

To explore the potential 'enrichment' of the data, we compare the OLT sub-groups using unadjusted Kaplan-Meier (KM) plots of time to first observed BOHE stratified by subgroup. The subgroups are roll-over, crossover, and new subjects.

Differences in KM survival curves were explored with log rank tests (with Mantel-Haenszel and Peto-modified Gehan-Wilcoxon statistics) using the null hypothesis that the survival curves between strata are the same. Alpha was set at the conventional 0.05 level.

2.1.5 Analysis

Three analyses are presented:

1. comparison of time to first observed BOHE from RFHE3002 baseline for rollover, crossover and new patients;
2. comparison of time to first observed BOHE between RFHE3001 treatment groups and RFHE3002 subgroups, from each respective study baseline; and
3. comparison of time to first BOHE event between new rifaximin naïve entrants to RFHE3002 with the combined RFHE3001 & RFHE3002 data for rollover and crossover patients.

2.1.5.1 RFHE3002 Open-label Subgroups

Figure 3 suggests that there is a slight improvement in event-free survival (time to first observed BOHE) in the crossover and roll-over groups compared with the new subjects group, more so for the

crossover group. Whilst there are subtle visual differences between the groups, there is no statistically significant difference.

Log rank tests (Panel 1) of difference in survival curves for new subjects and for subjects rolled-over from RFHE3001 yield a $p > 0.05$, suggesting that the null hypothesis that the survival curves are the same cannot be rejected.

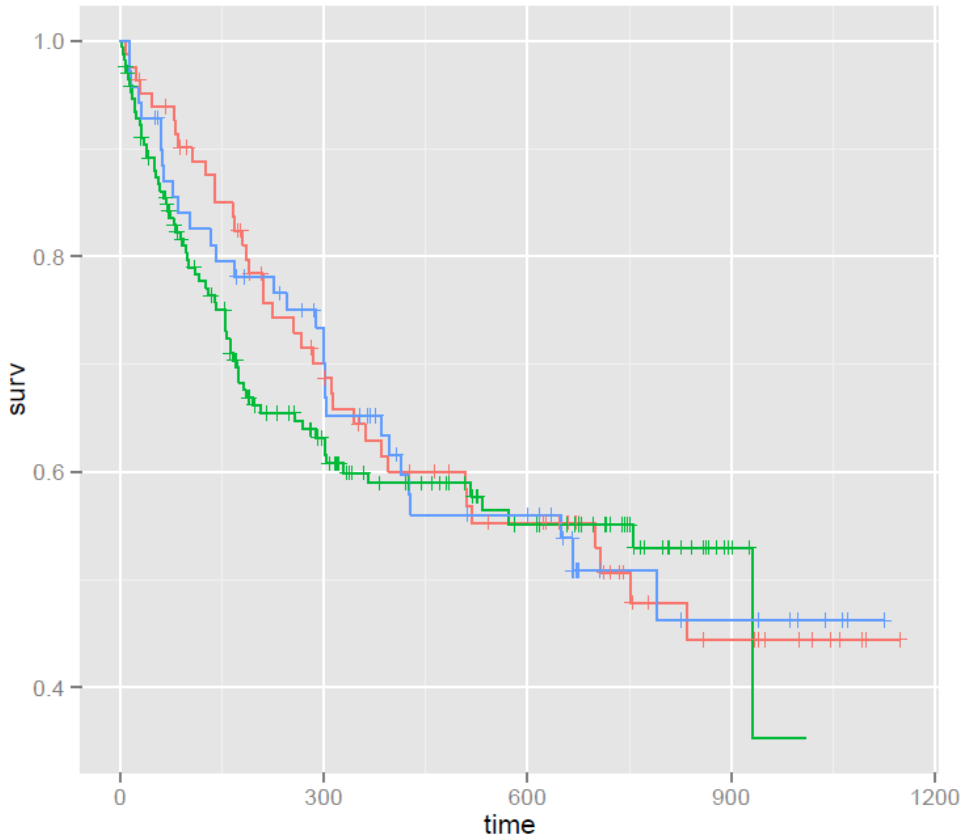


Figure 3. Unadjusted KM plots of time to first BOHE event stratified by OLT subgroup (red, 3001 placebo crossover; green, 3002 new; blue, 3001 rifaximin rollover)

```
Call:
survdiff(formula = Surv(T_BOHE, BOHE) ~ GROUP, data = df5[first3002 &
    df5$GROUP != "RIF_CONT_3002", ])

                       N Observed Expected (O-E)^2/E (O-E)^2/V
GROUP=RIF_ROLL_3002   70       31     32.0    0.0329    0.0433
GROUP=RIF_NEW_3002   169       67     64.3    0.1158    0.2230
GROUP=RIF_CROSS_3002  82       37     38.7    0.0749    0.1054

 Chisq= 0.2  on 2 degrees of freedom, p= 0.893

Call:
survdiff(formula = Surv(T_BOHE, BOHE) ~ GROUP, data = df5[first3002 &
    df5$GROUP != "RIF_CONT_3002", ], rho = 1)

                       N Observed Expected (O-E)^2/E (O-E)^2/V
GROUP=RIF_ROLL_3002   70     23.3     24.6    0.0725     0.119
GROUP=RIF_NEW_3002   169     54.7     50.5    0.3523     0.854
GROUP=RIF_CROSS_3002  82     26.8     29.6    0.2801     0.493

 Chisq= 0.9  on 2 degrees of freedom, p= 0.642
```

Panel 1. Log-rank test syntax and results for RFHE3002 subgroup comparison of time to first observed BOHE

2.1.5.2 Comparison of RFHE3001 Treatment Groups with RFHE3002 Subgroups

The previous section (2.1.5.1) suggested that there were no significant differences between the subgroups in the OLT in time to first observed BOHE. To further explore potential 'enrichment' of data we compared the OLT subgroups with the RCT treatment allocation (placebo and rifaximin) using unadjusted KM plots of time to first observed BOHE stratified by subgroup.

Figure 4 suggests that while there is an expected difference between the placebo and the rifaximin treatment groups in RFHE3001, there is very little difference between RCT rifaximin subjects and OLT newly recruited subjects. In line with the findings of the previous section, there is some visual improvement in event-free survival in crossover and roll-over groups compared with new patients but no statistically significant difference.

Log-rank tests (Panel 2) between survival curves for subjects treated with rifaximin in RFHE3001 and newly recruited subjects treated with rifaximin in RFHE3002 yields a $p > 0.05$, suggesting that the null hypothesis that the survival curves are the same cannot be rejected.

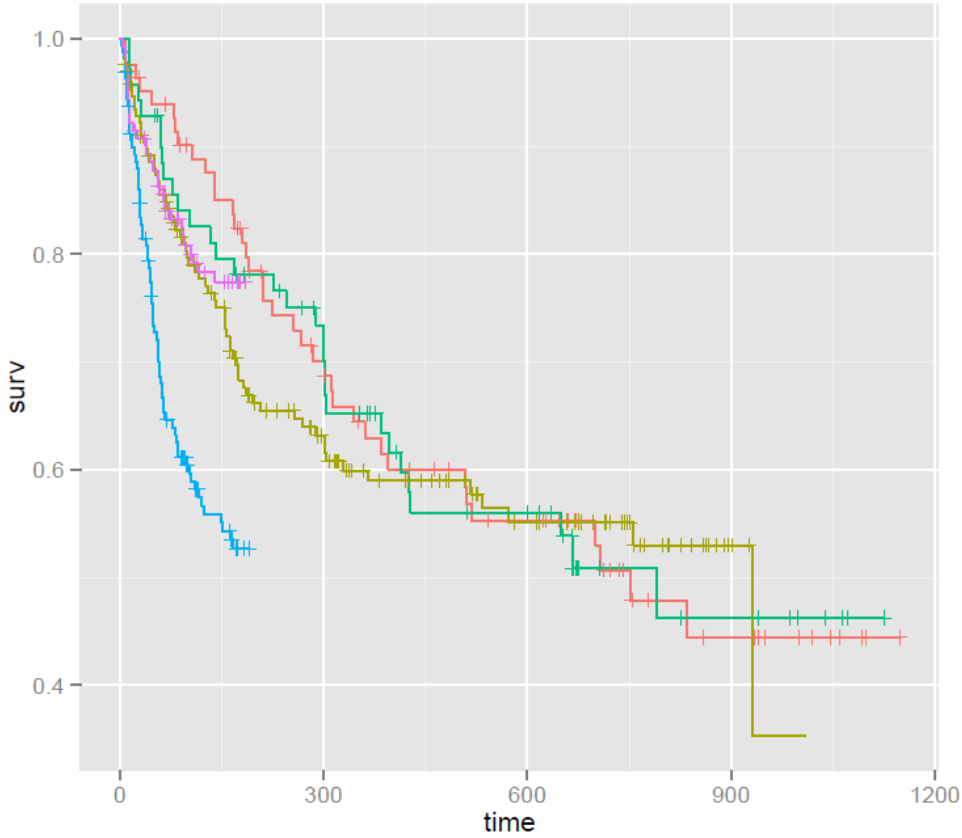


Figure 4. Unadjusted KM plots of time to first observed BOHE event stratified by RCT and OLT subgroup (blue, 3001 placebo; purple, 3001 rifaximin; olive green, 3002 new; red, 3002 placebo crossover; green, 3002 rifaximin rollover).

```
Call:
survdiff(formula = Surv(T_BOHE, BOHE) ~ GROUP, data = df5[first &
    (df5$GROUP == "RIF_3001" | df5$GROUP == "RIF_NEW_3002"),
    ])

                     N Observed Expected (O-E)^2/E (O-E)^2/V
GROUP=RIF_3001     140       30     34.8     0.675      1.22
GROUP=RIF_NEW_3002 169       67     62.2     0.378      1.22

 Chisq= 1.2  on 1 degrees of freedom, p= 0.268

Call:
survdiff(formula = Surv(T_BOHE, BOHE) ~ GROUP, data = df5[first &
    (df5$GROUP == "RIF_3001" | df5$GROUP == "RIF_NEW_3002"),
    ], rho = 1)

                     N Observed Expected (O-E)^2/E (O-E)^2/V
GROUP=RIF_3001     140     26.9     30.5     0.421      0.87
GROUP=RIF_NEW_3002 169     53.6     50.1     0.256      0.87

 Chisq= 0.9  on 1 degrees of freedom, p= 0.351
```

Panel 2. Log-rank test syntax and results for RFHE3002 'NEW' subgroup and RFHE3001 'RIFAXIMIN' treatment group comparison of time to first observed BOHE.

2.1.5.3 Combined Rifaximin versus OLT Subgroups

Figure 4 illustrated the differences in follow up time between RFHE3001 and RFHE3002. As a final comparison, the data from RCT rifaximin, OLT roll-over, and OLT cross-over groups were combined and compared with the other OLT subgroups (crossover and new patients) using unadjusted KM plots of event-free survival stratified by subgroup (Figure 5). Note that all survival curves are from first rifaximin dose to censor/event date. Therefore, roll-over rifaximin subjects are followed during both RFHE3001 and RFHE3002 where applicable.

Again, there is a slight visual improvement in the new subjects but there is no statistically significant difference.

Log-rank tests (Panel 3) between survival curves for new subjects, crossover subjects and rollover subjects yield a $p > 0.05$, suggesting that the null hypothesis that the survival curves are the same cannot be rejected.

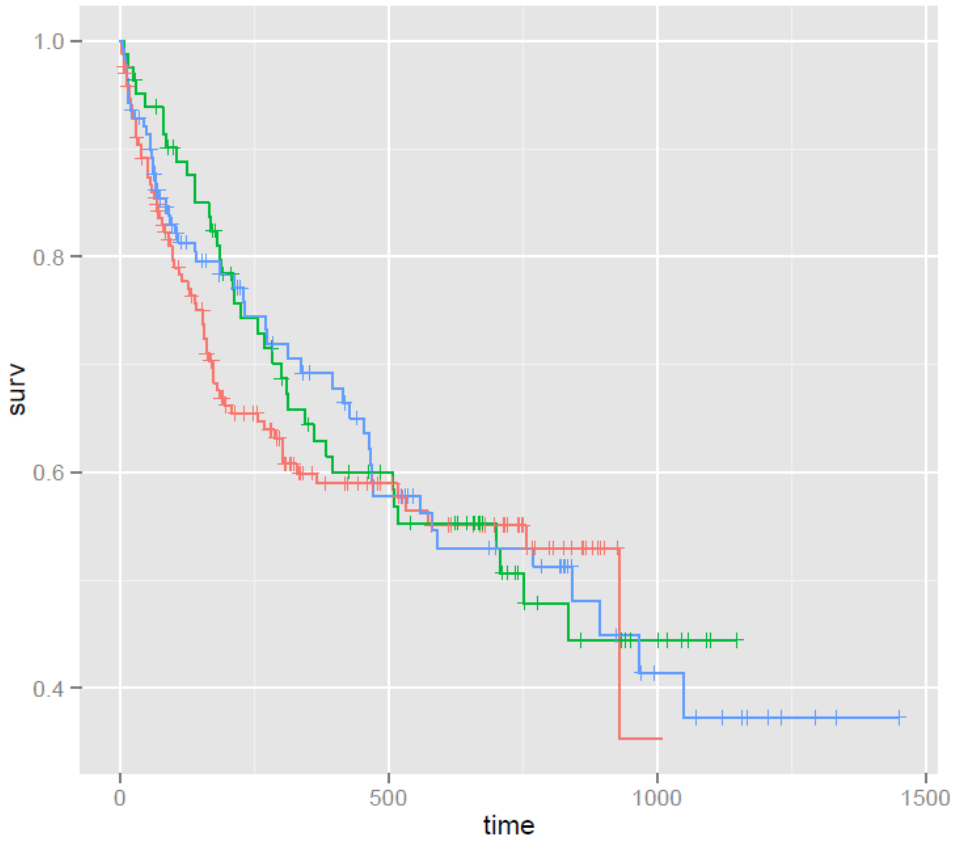


Figure 5. Unadjusted KM plots of time to first observed BOHE event stratified by OLT subgroup using combined RCT and OLT data (red, RFHE3002 new; green, placebo crossover [combined RFHE3001 & RFHE3002]; blue, rifaximin rollover [combined RFHE3001 & RFHE3002]).

```
Call:
survdiff(formula = Surv(T_BOHE, BOHE) ~ GROUPc, data = df5[firstConcRif01,
    ])

                        N Observed Expected (O-E)^2/E (O-E)^2/V
GROUPc=RIF_3001+3002  140       51     47.7  0.233359  0.341431
GROUPc=RIF_CROSS_3002  82       37     40.2  0.255051  0.347938
GROUPc=RIF_NEW_3002   169       67     67.1  0.000263  0.000468

 Chisq= 0.5  on 2 degrees of freedom, p= 0.78

Call:
survdiff(formula = Surv(T_BOHE, BOHE) ~ GROUPc, data = df5[firstConcRif01,
    ], rho = 1)

                        N Observed Expected (O-E)^2/E (O-E)^2/V
GROUPc=RIF_3001+3002  140     40.9     38.1     0.195    0.3528
GROUPc=RIF_CROSS_3002  82     26.3     30.6     0.594    1.0097
GROUPc=RIF_NEW_3002   169     53.9     52.4     0.045    0.0987

 Chisq= 1.1  on 2 degrees of freedom, p= 0.589
```

Panel 3. Log-rank test syntax and results for combined rifaximin group, crossover patients and new patients to RFHE3002 comparison of time to first observed BOHE

2.1.6 Key Results

These findings suggest that event-free survival (time to first observed BOHE) in the roll-over and crossover subjects of RFHE3002 is not significantly different. The newly recruited subjects in the OLT study are a very close match to those in the rifaximin arm of the RCT in terms of event-free survival.

2.1.7 Discussion

The evidence from this comparison indicates that time to first observed BOHE is comparable between RCT and OLT subjects, as expected from the similarity in baseline characteristics[F] [3,4]. Although RFHE3002 data is not used for modelling transition to first observed BOHE ($Covert_1$ to $Overt_1$) in line with the Committee's recommendation, confidence in the representativeness of RFHE3002 supports use the OLT data for the modelling of mortality and subsequent BOHE events in newly-recruited subjects.

2.1.8 Summary of Key Findings

- There is no statistically significant difference in event-free survival (time to first observed BOHE) from first OLT rifaximin dose between either rollover, crossover, or new rifaximin treated subjects in RFHE3002,
- Time to first observed BOHE between rifaximin treated patients in RFHE3001 and new rifaximin treated patients in RFHE3002 are visually identical and not statistically different,

[F] With the exception of number of prior HE episodes: RFHE3002, ≥1 prior HE episode in the preceding 12 months; RFHE3001, ≥2 prior HE episode in the preceding 6 months.

- There is no statistically significant difference in time to first observed BOHE from first rifaximin dose between either rollover (first dose in RFHE3001), crossover (first dose in RFHE3002), or new rifaximin treated subjects in RFHE3002.

2.2 First and Subsequent Transitions from Covert to Overt HE States

2.2.1 Executive Summary

The Committee (ACD[1] section 3.37) criticised the choice of survival models used to predict BOHE in the original economic modelling. The use of combined data from RFHE3001 & FRHE3002 to model time to first observed BOHE in the rifaximin arm but only RFHE3001 data for the placebo arm appeared to introduce uncertainty as evidenced by the ICER which varied up to twofold depending on the choice of survival distribution. Also, the assumption of a constant hazard over time for modelling subsequent HE events was felt to be clinically unrealistic. In validation of the original modelling of time to first observed BOHE from RFHE3001 data the log-normal distribution offers the best fit. Using RFHE3002 data for new patients only to model time to subsequent BOHE it was found that event failure accelerates with increasing event order. A combined analysis of all subsequent BOHE, consistent with the structure of the economic model, was also best fitted by a log-normal parametric survival model.

2.2.2 Methods Overview

Within the economic model, BOHE is modelled in two phases. Initial covert to first observed overt state transition (C_1 to O_1) relates to time to first observed BOHE, the primary efficacy endpoint of the RFHE3001 study. Following recovery from O_1, and transition to a subsequent covert state (C_2), time to all subsequent overt HE states (O_2) is modelled with a single separate function.

Time to first observed BOHE (C_1 to O_1) was originally modelled using parametric proportional hazards survival analysis and candidate distribution families including either one of exponential, Weibull, Gompertz, log-normal, and log-logistic. In the original submission, the survival curves were extrapolated beyond 168 days for both groups using a log-normal distribution, which were considered to provide the best model fit based on Akaike and Bayesian information criteria (AIC and BIC respectively) and visual inspection. However, the ERG suggested that the Gompertz distribution provided the best model fit to extrapolate the time to the first BOHE when the RFHE3001 data were used. The use of the Gompertz distribution is questionable as the shape of the survival curve, which becomes horizontal after 24 months, seems contrary to clinical expectation of the natural history of the disease.

Therefore, a key objective for Norgine was to independently check which distribution best fits time to first HE event in the RFHE3001 RCT data.

Given that time to subsequent episodes was not available from RFHE3001, transition from a subsequent covert to a subsequent overt state (C_2 to O_2) was originally modelled using data on time to first breakthrough episode, applying an exponential distribution and extrapolating to 5 years. Also the treatment effect of rifaximin was assumed to be constant for all subsequent BOHE. Previously, the hazard ratio (HR) for rifaximin compared with placebo was derived from the resulting parameter estimates and applied to the baseline survivor function (placebo) to estimate the survivor function

for rifaximin. This assumed that the risk of having a subsequent BOHE was independent of the risk of preceding episodes and the time spent in the remission state. It was also assumed that the risk reduction for the first breakthrough episode could be applied to subsequent episodes and was further assumed to be constant over time for subsequent episodes.

The ERG stated, based on their clinical experts' opinion, that the assumption of a constant probability of subsequent episodes over time did not reflect reality. The impact of this assumption was not easily foreseen and may be a potential driver of uncertainty in the ICER estimated. There was further concern that using an exponential distribution, implying a constant and proportional hazard between treatment arms, did not appear to be a good fit to the data based on visual inspection, AIC and BIC.

Therefore, an additional key objective for Norgine was to fully explore subsequent BOHE using data from the open-label RFHE3002 study.

2.2.3 Study Population

Validation of the time to first observed BOHE was conducted using the primary efficacy endpoint data from the intention-to-treat (ITT) population of the RFHE3001 study.

Exploration of time to subsequent observed BOHE was conducted using data from the open-label RFHE3002 study using all HE events excluding the first observed HE event. The OLT data, rather than the RCT data, was analysed as the RCT did not record recurrent observed HE events unlike the OLT. Based on the findings of the previous analysis (section 2.1.5.2) that the RCT and OLT were comparable in terms of time to first observed BOHE, the assumption was made that they should also be comparable in time to subsequent BOHE (had RFHE3001 'event-failures' been further followed). In this analysis, only new rifaximin treated subjects from the OLT were used because whilst previous findings suggest that it would be reasonable to use the whole OLT dataset, the newly recruited subjects were almost identical in terms of time to first observed BOHE and also because this would isolate the results from any potential enrichment bias.

2.2.4 Methods (Including Statistical Methods)

Time to first observed BOHE was modelled using parametric survival modelling with a single covariate indicating treatment group membership (rifaximin or placebo) and survival times were right-censored at 170 days[3]. Proportional hazards (PH) parameterisation is used for the specified distributional families.

Time to subsequent BOHE was also modelled using parametric PH survival modelling and the new patient data from RFHE3002. Because all subjects in the OLT were treated with open-label rifaximin, there was no placebo arm in the OLT data. In order to model time to subsequent BOHE in both the rifaximin and placebo groups, the primary efficacy treatment effect for rifaximin observed in RFHE3001 (section 2.2.5.1) was applied to all subsequent events. PH parameterisation is used for the specified distributional families.

2.2.5 Analysis

2.2.5.1 Covert to Overt Transition (C_1 to O_1)

Five parametric survival models were fitted to the RCT data, one for each candidate distribution. Goodness of fit of the models to the data was assessed both statistically and graphically. Table 1 ranks the models by log likelihood where smaller negative log likelihood indicates a better fit to the data.

Table 1. Parametric model fits ranked by log likelihood (C_1 to O_1 transition).

Distribution	Model	LogLikelihood	Rank
Log Normal	f.ln	-748.678492716891	1.00
Log Logistic	f.ll	-752.934826964358	2.00
Weibull	f.w	-755.581081717404	3.00
Exponential	f.e	-758.556457601173	4.00
Gompertz	f.g	-758.556457602919	5.00

Model fit was also visually assessed by fitting a semi-parametric Cox PH model (which makes no assumptions on the underlying distribution) and plotting the cumulative hazard function of the parametric and semi-parametric models for comparison. Figure 6 confirms the previous result that the log normal distribution is the best fit for the data.

Using the fitted log normal distribution the predicted survival probabilities (S_t) were calculated for use as input parameters to the economic model.

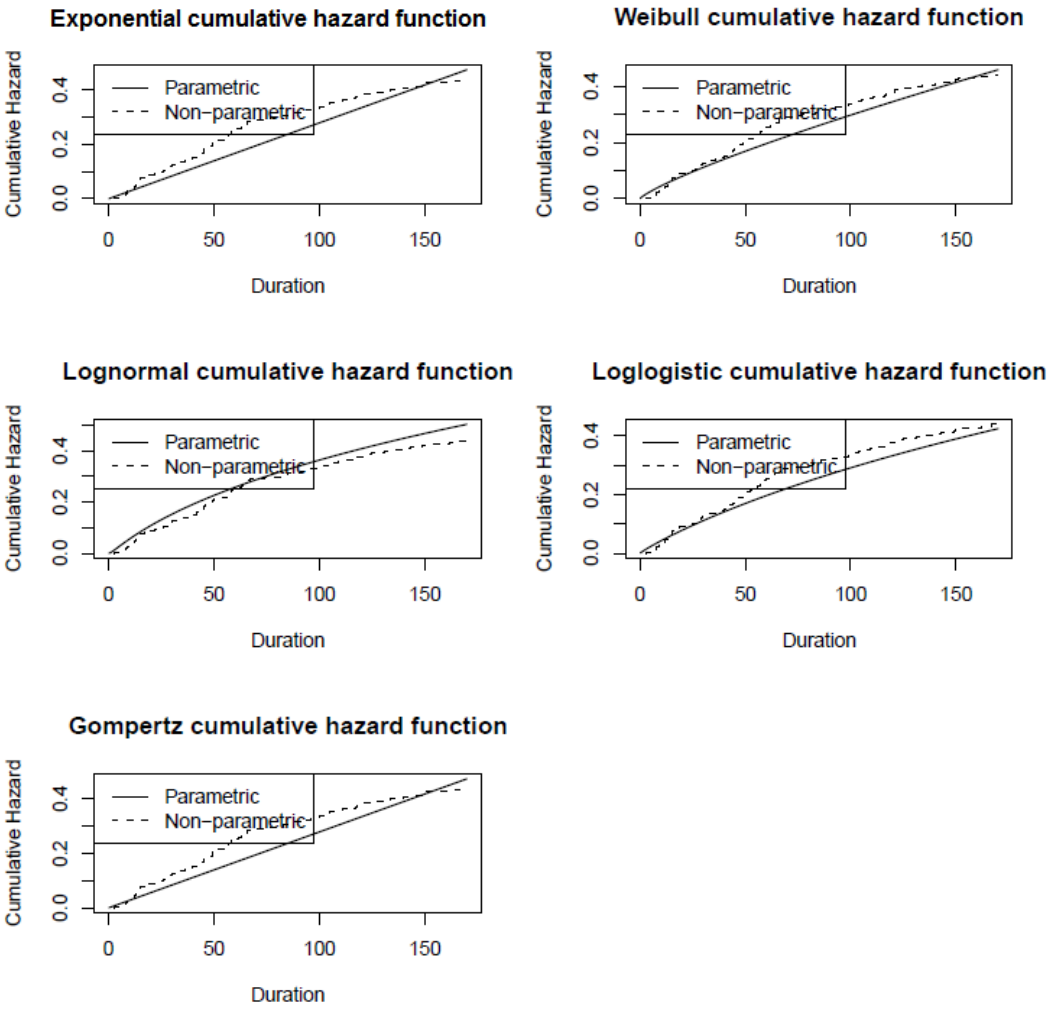


Figure 6. Parametric and semi-parametric cumulative hazard function by distribution (C_1 to O_1 transition)

2.2.5.2 Subsequent Covert to Subsequent Overt Transition (C_2 to O_2)

2.2.5.2.1 Non-parametric estimation

[redacted](Figure 7) [redacted](Figure 8).

[redacted](Figure 9 & Figure 10).

[redacted]

Figure 7. Unadjusted Kaplan Meier survival curves for time to BOHE stratified by event cardinality

[redacted]

Figure 8. Unadjusted Kaplan Meier survival curves for time to BOHE stratified by event cardinality. Subjects that have ≤30 days between subsequent events have been removed.

[redacted]

Figure 9. Unadjusted Kaplan Meier survival curves for time to BOHE categorised as first or combined subsequent.

[redacted]

Figure 10. Unadjusted Kaplan Meier survival curves for time to BOHE categorised as first or subsequent. Subjects that have ≤30 days between subsequent events have been removed.

2.2.5.2.2 Parametric Modelling

The objective of this section was to independently check which distribution best fits time to subsequent BOHE in the RFHE3002 data, using only the newly recruited subjects.

Five parametric survival models were fitted to the RFHE3002 data (new subjects only), one for each candidate distribution. The goodness of fit of the models to the data was assessed both statistically and graphically. Table 2 ranks the models by log likelihood where smaller negative log likelihood indicates a better fit to the data. The log normal distribution appears to offer the optimal fit to the RFHE3002 subsequent HE event data.

Table 2. Parametric model fits ranked by log likelihood (C_2 to O_2 transition)

Distribution	Model	LogLikelihood	Rank
Log Normal	f.ln	-377.199066664794	1.00
Log Logistic	f.ll	-377.801479763306	2.00
Weibull	f.w	-381.784930571138	3.00
Exponential	f.e	-388.571074379557	4.00
Gompertz	f.g	-388.572136484095	5.00

Model fit was also visually assessed by fitting a semi-parametric Cox PH model and plotting the cumulative hazard functions of the parametric and semi-parametric models for comparison. Figure 11 confirms the previous result that the log normal distribution is the best fit to the data.

Using the fitted log normal distribution the predicted survival probabilities (S_t) were calculated for use as input parameters to the economic model.

[redacted]

Figure 11. Parametric and semi-parametric cumulative hazard function by distribution (C_2 to O_2 transition)

2.2.6 Key Results

The re-analysis of RFHE3001 time to first BOHE confirms the log-normal distribution as the best fit of the data. The Gompertz distribution is the poorest fitting distribution of the available choices. The S_t extrapolation to a five-year horizon matches closely the RFHE3001 fitted model used in the original submission (Figure 12).

Comparison with the KM plot for new RFHE3002 patients confirms the log-normal fitted model of the RFHE3001 as the closest fit (Figure 13).

A log-normal distribution also provides the best fitting parametric model for combined time to subsequent BOHE. Figure 14 illustrates how the original exponential model fitted to the RFHE3001 data exaggerates the difference in S_t for placebo versus rifaximin.

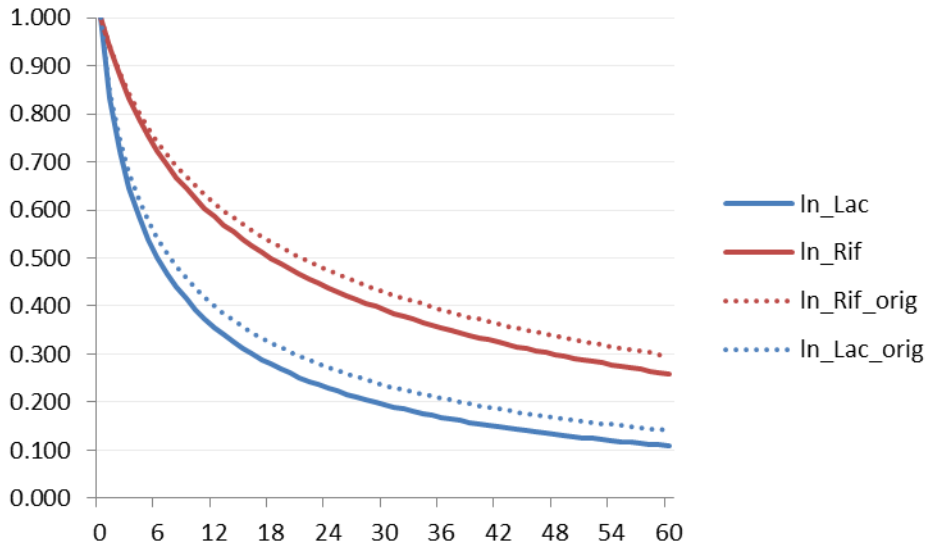


Figure 12. Comparison of original versus revised log-normal fitted parametric survival models for time to first observed BOHE from RFHE3001 data

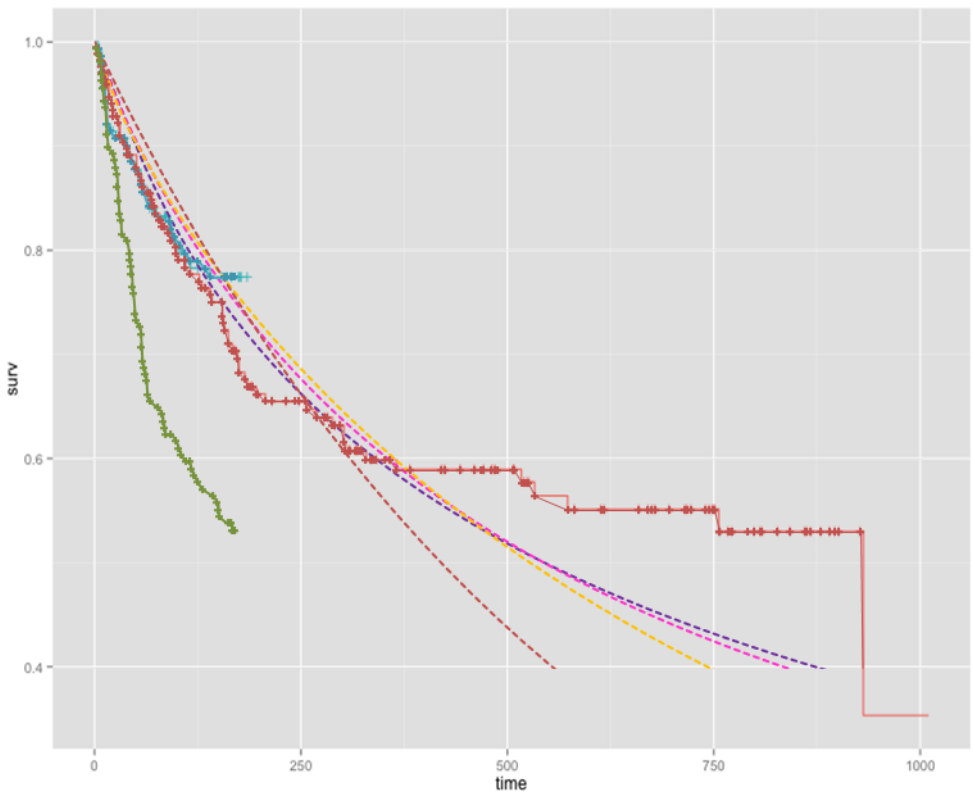


Figure 13. Comparison of fitted models to KM-survival plots for time to first observed BOHE (blue, 3001 rifamixin [KM]; pink dashes, 3001 rifaximin [loglogistic fitted]; red line, 3002 new patients [KM]; yellow dashes, 3001 rifaximin [weibull fitted]; purple dashes, 3001 rifaximin [log-normal fitted]; brown dashes, 3001 rifaximin [exponential fitted]; green, 3001 lactulose [KM])

[redacted]

Figure 14. Comparison of original vs. revised fitted models for transition from C_2 to O_2 (including revised fitted C_1 to O_1 transition)

2.2.7 Discussion

A log-normal parametric survival model of time to first observed BOHE fitted to the RFHE3001 primary endpoint data is confirmed as the optimal model and is therefore selected as the base-case model for extrapolation of RFHE3001 6-month data to a five-year economic model horizon.

The ERG conclusion that the assumption of a constant probability of subsequent episodes over time did not reflect reality appears justified by the non-parametric analysis of subsequent BOHE showing decreasing time to failure with increasing event cardinality.

The model structure specifies a single combined subsequent covert to overt sequence. Therefore, a simplified parametric survival function fitted to all combined subsequent events from RFHE3002 (also with a log-normal distribution) has been developed and incorporated into the revised economic model. The treatment effect for rifaximin over placebo has been applied as a constant to the S_t for the placebo arm.

2.2.8 Key Findings

- Time to first BOHE in the RFHE3001 data is optimally modelled using the log-normal distribution as the best fit of the data. The Gompertz distribution is the poorest fitting distribution of the available choices.
- Comparison with the KM plot for new RFHE3002 patients confirms the log-normal fitted model of the RFHE3001 as the closest fit.
- A log-normal distribution also provides the best fitting parametric model for combined time to subsequent BOHE.

3 Use of Utilities in the Cost-effectiveness Model

3.1 Executive Summary

The reliability of utilities estimated from the general public was criticised by the Committee on the grounds that the values generated were much higher than and not representative of those seen in liver disease[13] - a condition known to have a severe detrimental impact on quality of life (QoL). The Committee questioned why Norgine had not used the QoL data collected during the RFHE3001 study. This section is a response to this request.

A validated algorithm was used to convert SF-36 observations into EQ-5D utility values. From these, a clear and robust relationship between Chronic Liver Disease Questionnaire (CLDQ) Overall score and estimated EQ-5D utility was demonstrated. A mean incremental utility of 0.106 was calculated by applying this function to the published QoL improvement demonstrated for rifaximin patients in the remission state[6].

3.1.1 Methods Overview

Published results from the RFHE3001 data[6] showed that in the covert remission state the rifaximin-treated patients experienced an incremental improvement in QoL as measured by the CLDQ over those receiving placebo (Figure 15).

In this section the objective was to estimate EQ-5D utility from QoL data available in RFHE3001 for rifaximin and placebo treated ITT patients during remission.

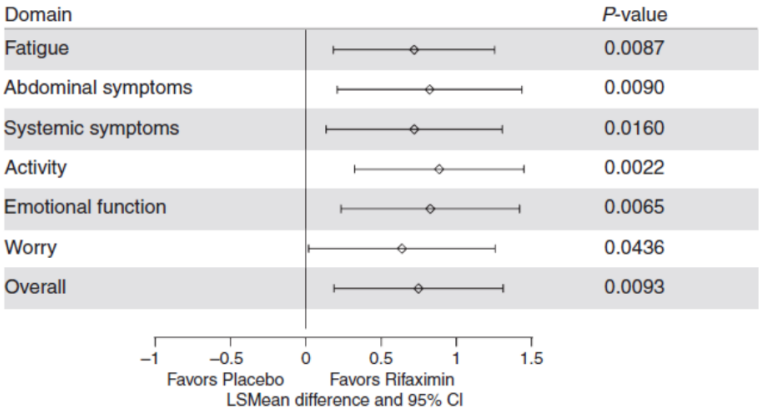


Figure 15. Chronic Liver Disease Questionnaire Domain Scores – rifaximin vs. placebo. Differences in least square (LS) means of time-weighted average values and corresponding 95% confidence intervals for subjects in the rifaximin vs. placebo groups are presented for the six CLDQ domain scores and for the overall CLDQ score. Least square mean values are illustrated with diamonds and 95% confidence intervals are illustrated with brackets to the left and right of the LS mean. An analysis of variance (ANOVA) model with effects for treatment was used to calculate P-values (reproduced from Sanyal et al[6], orig. Figure 3).

3.1.2 Study Population

For this analysis QoL data from Canadian & USA patients enrolled to the RFHE3001 RCT were used. Russian patients were ineligible for this analysis as there was no validated Russian translation of the CLDQ available.

3.1.3 Methods (Including Statistical Methods)

Conversion of SF-36 data into EQ-5D utilities was performed using the response mapping algorithm developed by Gray et al[14]. Rather than estimating final EQ-5D score directly, the algorithm predicts the ordinal response level to each of the five EQ-5D dimensions from the observed responses to the SF-12 subset of the SF-36.v1 questionnaire.

The mapping algorithm makes no allowance for missing values in the SF-12 input data and of the 1,332 completed SF-36 questionnaires, 14% were found to have at least one missing question response. Correction of all missing SF-12 values was successfully performed with [redacted]

In line with Gray's recommendation for application of the response mapping algorithm to small samples, 250 replications using Monte Carlo simulation were made applying default UK tariff [16] and the mean EQ-5D utility was used to represent each QoL observation.

Exploratory analysis of the relationship between Overall CLDQ score and estimated EQ-5D index utility was performed with regression analysis applying linear, logarithmic, cubic and quadratic functions to determine best curve fit.

[redacted]modelling with repeated subject measures, a normal ********** was then used to quantify the relationship between Overall CLDQ score and estimated EQ-5D index utility.

The [redacted] parameter estimate for CLDQ was then applied to baseline CLDQ Overall score, to the incremental improvement in CLDQ QoL reported for rifaximin patients whilst observed in remission, and also to the CLDQ scores recorded for QoL observations made whilst in the overt state.

[redacted]

Figure 16. Diagrammatic representation of methodology for EQ-5D utility estimation from RFHE3001 QoL data.

3.1.4 Analysis

3.1.4.1 Curve Estimation

Unadjusted regression of CLDQ Overall score to estimated EQ-5D index utility (Figure 17) shows the clear relationship between the two. Whilst the cubic or quadratic functions have the highest explanatory power (R^2 = 0.590; Table 3) the linear function is only marginally lower with 58.7% of variation in EQ-5D utility explained by CLDQ Overall score.

Figure 17. Regression plots for SF-12 estimated EQ-5D utility as a function of observed Overall CLDQ score

Table 3. Curve estimation summaries for regression of estimated EQ-5D utility to observed Overall CLDQ score

3.1.4.2 Repeated Measures Analysis

The [redacted] modelling on 874 paired CLDQ and EQ-5D observations showed CLDQ Overall score as a significant predictor (p<0.001) of estimated EQ-5D utility. Each additional unit CLDQ score confers an incremental utility of [redacted] Table 4).

Table 4. Summary of General Estimating Equations model of EQ-5D (dependent) as a function of Overall CLDQ with repeated subject measures.

[redacted]

3.1.4.3 Baseline CLDQ Summary

There was no difference (p=0.913) in CLDQ Overall score at baseline for patients allocated to either rifaximin or placebo. The overall baseline mean for all ITT patients was 4.11.

Table 5. Comparison of between-group differences in Overall CLDQ at baseline for rifaximin and placebo treated patients in RFHE3001

Group Statistics

	TRTN	N	Mean	Std. Deviation	Std. Error Mean
CLDQALL	0	105	4.12161754	1.197032635	.116818424
	1	94	4.10341307	1.147780240	.118384493

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
CLDQALL	Equal variances assumed	.050	.823	.109	197	.913	.018204468	.166705714	-.310552375	.346961312
	Equal variances not assumed			.109	196.059	.913	.018204468	.166317264	-.309796045	.346204982

3.1.4.4 Covert/Overt CLDQ Summary

A small number of CLDQ observations (N=67) were made on or after the date of BOHE with a mean value of 3.76 (Table 6), lower than that observed at baseline.

Table 6. Mean CLDQ Overall score for QoL observations made on or after the recorded date of BOHE.

Report

CLDQALL

Mean	N	Std. Deviation
3.76295601	67	1.019383899

3.1.5 Key Results

Applying the EQ-5D utility conversion factor obtained from GEE modelling to observed CLDQ scores, the following health state utilities can be imputed (Table 7).

The baseline remission state utility can be valued at [redacted] assumed to continue for the placebo group whilst in remission. Applying the incremental least-squares mean improvement in CLDQ reported by Sanyal[6] (0.743 unit score), rifaximin patients can be estimated to have a utility whilst in remission of [redacted]

For those CLDQ observations made in the overt state, the mean derived utility is [redacted]

Table 7. Derived EQ-5D utilities for model health states based on observed CLDQ Overall scores.

		Mean	SD	N		EQ-5D
COVERT	CLDQ-baseline	4.11	1.17	199		[redacted]

		Mean	LCL	UCL		Mean	LCL	UCL
COVERT	CLDQ-rifaximin	4.85	4.29	5.41		[redacted]	[redacted]	[redacted]
	CLDQ-lactulose	4.11				[redacted]		
					delta	0.106	0.026	0.186

		Mean	SD	N	
OVERT	All	3.76	1.02	67	[redacted]

3.1.6 Discussion

Health state utility (the EQ-5D index) has been estimated from generic QoL observations (SF-36) collected during the pivotal RFHE3001 study using an established conversion algorithm. Furthermore, estimated EQ-5D utility is correlated with disease-specific QoL as measured by the CLDQ Overall score. Application of this relationship to observed CLDQ values from the RCT has allowed derivation of health state utility values for the remission state in line with published data for patients with HE where a value of 0.55 ± 0.22 has been reported[17]. The disutility derived from CLDQ observations in the overt state is likely conservative as QoL questions would only be completed by those with less severe episodes.

3.2 Key Findings

- Following correction for missing data, SF-36 observations from the RFHE3001 study were successfully used to estimate EQ-5D utility,
- A significant near-linear relationship between CLDQ Overall score and estimated EQ-5D utility was demonstrated,
- Applying this relationship to the incremental improvement in CLDQ reported for rifaximin patients in the remission state, an incremental utility for rifaximin of 0.106 was shown.

4 Mortality

4.1 Executive Summary

In the original submission, modelled mortality was criticised (ACD[1] Section 4.9) as being a poor reflection of clinical experience yet was found to be the key driver of cost-effectiveness despite no observed mortality benefit in the RCT. In the previous base-case approximately 50% of the model population died over a 6-month period compared with 7% (21 deaths) in RFHE3001. There were also concerns that the model predicted a 5% reduction in the risk of mortality with rifaximin compared with placebo during the first 6 months of the model that had not been observed between the treatment groups in RFHE3001, and for which no other definitive evidence existed.

In this section, Norgine describe the review of literature for mortality of HE patients with liver cirrhosis and the new analysis of CPRD, to contextualise a further analysis of the OLT.

Data from the OLT was used to model four mortality functions consistent with the economic model. Each function is substantially more conservative than those used in the original economic modelling.

The revised model predicts mortality in line with that observed in the OLT, reported in literature and observed in UK clinical practice for 'recurrent' HE patients.

4.2 Methods Summary

In the previously submitted model, mortality was derived from England and Wales age-related mortality rates applied to the RFHE3001 study population supplemented by HE specific rates from the published studies from Spain[9] and the UK[11].

In this section, we review the published evidence on mortality in patients with HE and describe analysis of mortality observed among patients in RFHE3002.

The analyses are conducted with the four Markov states of the economic model borne in mind and are ordered thus: time to death from the initial covert state; probability of mortality within 30-days of the first observed BOHE; time to death from the subsequent covert state; and probability of mortality within 30-days of any subsequent observed BOHE.

4.2.1 Review of Published Studies and Commissioned Analysis of CPRD Data

A review of literature relating to mortality in patients with HE and an analysis of HE related mortality commissioned via the CPRD were conducted[18] in line with analyses of mortality from the RFHE3001[3] and RFHE3002 studies[4].

4.2.1.1 Literature Review

Fourteen studies where HE related mortality were identified are included in section 6 of the mortality report[10].

4.2.1.1.1 Mortality rates over time

Reviewing the publications that refer to mortality over time [10], it is apparent that the studies have disparate designs, inclusion/exclusion criteria and a wide range of patient characteristics; making

direct comparisons difficult. However, one common factor across these publications was the inclusion of patients at the first event of interest, that is, they were inception cohorts.

Mortality at 6 months in patients with HE ranged from 16% in patients hospitalised with Conn score 1 to 61% hospitalised with Conn score 2. It was possible to calculate the 6 month mortality in two other papers by Jepsen et al[19] 2010 and Bustamante et al[9] 1999 as 42% and 52% respectively. In addition, a UK study of emergency ICU admissions of patients with HE Conn score 3 or 4 reported that one month mortality exceeded 50%.

4.2.1.1.2 In-hospital mortality[10]

Five publications were identified that reported in-hospital mortality without a specific time period. In 4 of the 5 studies the in-hospital mortality was high and ranged between 30% to 48%. Overall, these publications and the studies by Shawcross et al[11] and Stewart et al[20] indicate that hospitalisation or ITU admission result in high rates of mortality and further support the avoidance of hospitalisation for patients who have recurrent hepatic encephalopathy.

4.2.1.1.3 Differential mortality in rifaximin studies[10]

Two recent publications, Neff et al[21] and Vlachogiannakos et al[22] reported mortality rates in patients with chronic cirrhosis who were maintained on rifaximin (only a subset had HE in the Vlachogiannakos study).

Neff et al recently published an abstract of a retrospective observational study comparing outcomes, including mortality, in patients treated with lactulose, rifaximin or the combination. The results in Table 8 demonstrate that treatment with rifaximin alone compared to lactulose alone shows improvements in short and long-term survival in patients suffering from overt HE.

Table 8. Mortality rates in patients with HE treated with rifaximin, lactulose or the combination (adapted from Neff et al 2012[21])

Group	6 months	One year	3 years	P (vs LAC)
LAC (n=58)	40%	54%	71%	
LAC/RFX (n=55)	35%	46%	59%	0.057
RFX (n=28)	24%	37%	49%	0.049
None (n=44)	55%	65%	88%	

4.2.1.2 Mortality Analysis from CPRD 2013[18]

A retrospective analysis of the UK CPRD was commissioned to analyse data recorded between 1998-2012 on patients with liver disease, with a focus on a subset with HE. Of patients identified with HE, 304 of 551 (55.2%) died during the follow-up period compared with 6,693 of 16,479 (40.6%) of those without HE.

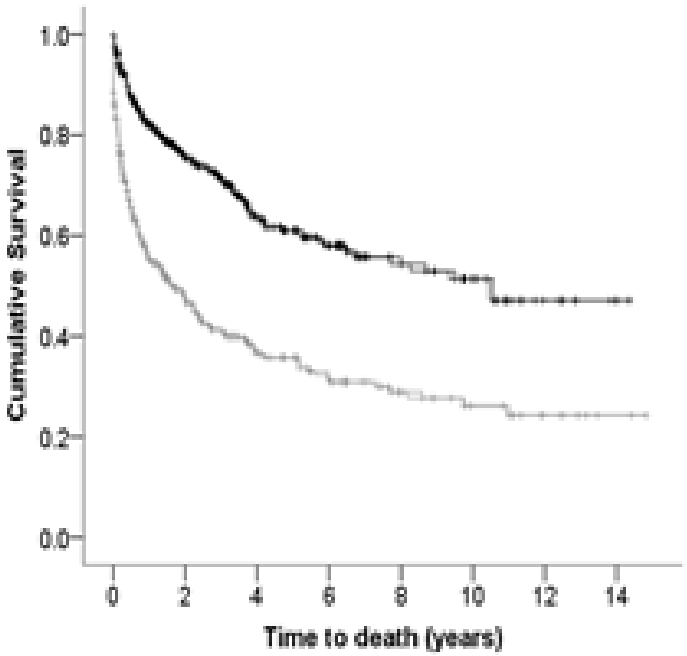


Figure 18. Time to death for patients diagnosed with liver disease failure and hepatic encephalopathy status compared with matched controls[18]

It can be seen from Figure 18 that there is a high initial mortality in the first 6-12 months; this appears to be associated with the first HE episode. The rates of mortality from CPRD (all grades) ranged from 32.2% at 6 months, 41.1% at 1 year through to 59.4% at 5 years[10].

This is in line with the 6 month mortality calculated from two other sources (Jepsen et al[19] [2010] and Bustamante et al[9] [1999]); 42% and 52% respectively.

4.2.1.2.1 Six-month Survivors

Based on these observations an additional analysis of the CPRD data was undertaken which included only patients who had survived 6 months after the index event, Figure 19. For those surviving six months following first HE recording the crude mortality rate was 96.4 per 1,000 patient years. Mortality at 6 months, 1, 3 and 5 years were also determined from this subset of HE patients. The data demonstrated that the mortality rates for HE patients with censoring at 6 months was substantially lower after this time point compared to the original time points without censoring[18]. The mortality rates in the CPRD 6 month survivors were similar to (up to 10% variance) the two rifaximin studies RFHE3001 and RFHE3002.

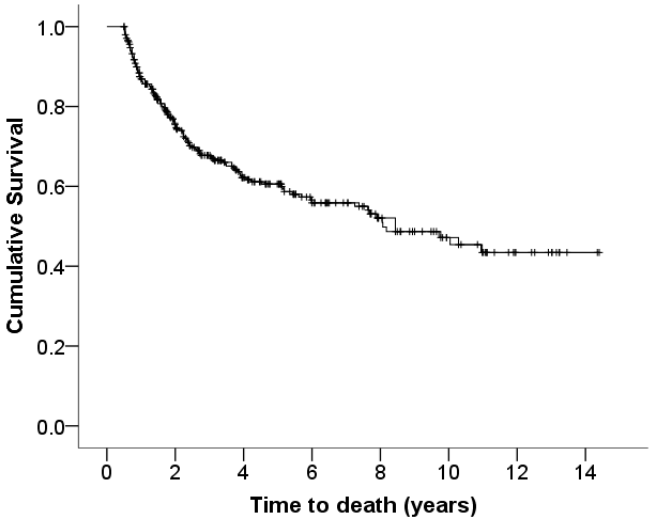


Figure 19. Time to death from recorded diagnosis of hepatic encephalopathy for those patients surviving six months after diagnosis.

4.2.1.3 Mortality in RFHE3001 and RFHE3002

RFHE3001 reported the mortality of HE patients at the end of the 6 month study. Patients were required to have at least 2 previous episodes of overt HE with a Conn score of ≥ 2 during the 6 months prior to enrolment. At baseline, the median time from diagnosis of first HE was 11.5 months (mean time 21.4 months). The mortality rate across the rifaximin and placebo groups (91% were on lactulose) was approximately 7% in both groups[3]

Patients enrolled in RFHE3002 had either completed study RFHE3001 (placebo or rifaximin treated subjects) or were new patients who had ≥ 1 verifiable episode of HE within 12 months prior to screening. At baseline, the median time from diagnosis of first HE was [redacted] The overall mortality for these patients was **** at 6 months **** at 1 year and *** ********* at 2 years[4]. Patients in RFHE3002 who continued treatment from RFHE3001 had similar rates of mortality to the RFHE3001 cohort of new patients.

The rates of mortality at 6 months in RFHE3001 and RFHE3002 are consistently lower than those reported in the above inception cohorts[10,18]. This is likely to be because the clinical trials recruited patients outside the initial harvest period for mortality.

4.2.2 Summary of Mortality Literature Review & CPRD Analysis Findings

- Patients in the UK experiencing their first HE event with decompensated liver cirrhosis have a particularly high level of mortality.
- Patients that are hospitalised with HE and a Conn score greater than 2 have a high level of mortality.
- Patients in RFHE3002 had survived the initial mortality risk of HE and hospitalisation, and experience a similar risk of mortality to those in the UK that have survived the initial six months after their first episode.

4.3 Incorporating Mortality from RFHE3002 into the Revised Economic Model

4.3.1 Executive Summary

Having demonstrated the representativeness of RFHE3002 data with respect to BOHE (first observed and subsequent episodes; section 2.1.5.2) and mortality of HE survivors (section 4.2.1.3), a series of revised survival functions were developed consistent with the structure of the economic model.

Modelled mortality in the revised model is a close approximation to that observed among survivors of a first HE episode.

4.3.2 RFHE3002 Study Population

Given a smaller number of deaths than BOHE, all patients from RFHE3002 were included in these analyses.

4.3.3 Methods (Including Statistical Methods)

Time to death from the covert state (C_1 and C_2) was analysed using parametric proportional hazards survival modelling. Proportional Hazards (PH) parameterisation is used for the specified distributional families. The index date for the initial covert state was the first open-label dose of rifaximin while for a combined dataset of subsequent events, the index was chosen as the 31st day following onset of the preceding BOHE event (i.e. when the model assumed recovery). For subjects whose next BOHE occurred less than 30-days after the previous episode the two neighbouring events were collapsed into a single 'pseudo-' event but maintained the 30-day recovery rule to set the index.

Probability of death whilst in the overt state was measured simply by counting the number of deaths within 30 days of onset of the first observed BOHE (O_1) and then similarly for combined subsequent BOHE events (O_2).

4.3.4 Analysis

4.3.4.1 Parametric Modelling: Covert (C_1) Mortality

Five parametric survival models were fitted to the OLT data, one for each candidate distribution. The goodness of fit of the models to the data was assessed both statistically and graphically. Table 9 ranks the models by log likelihood where a smaller negative log likelihood indicates a better fit to the data. The log normal distribution appears to offer the best fit to the data.

Next the visual fit of the model was assessed by fitting a semi-parametric model (Cox PH, which makes no assumptions on the underlying distribution) and plotting the cumulative hazard function the parametric and semi-parametric models for comparison. Figure 20 confirms the previous result that the log normal model is the best approximation of the data.

Using the fitted log normal model distribution, the predicted survival probabilities (S_t) were calculated for use as input parameters.

Table 9. Parametric model fits ranked by log likelihood (covert mortality)

Distribution	Model	LogLikelihood	Rank
Log Normal	f.ln	-219.924786691308	1.00
Log Logistic	f.ll	-221.11807630983	2.00
Weibull	f.w	-221.36136234199	3.00
Exponential	f.e	-221.402323188505	4.00
Gompertz	f.g	-221.402474652613	5.00

[redacted]

Figure 20. Parametric and semi-parametric cumulative hazard function by distribution (covert [C_1] mortality)

4.3.4.2 Overt (O_1) Mortality Calculation

Overt mortality was calculated as the proportion of subjects who entered the overt state that died within 30 days, namely [redacted]

4.3.4.3 Parametric Modelling: Subsequent Covert (C_2) Mortality

The objective of this section was to model time to death in the subsequent covert state in the OLT data. This was achieved by modelling the time to death using parametric survival modelling for the combined subsequent covert state. PH parameterisation is used for the specified distributional families.

Five parametric survival models were fitted to the OLT data, one for each candidate distribution. The goodness of fit of the models to the data was assessed both statistically and graphically. Table 10 ranks the models by log likelihood where a smaller negative log likelihood indicates a better fit to the data. In this instance the Weibull distribution appears to offer a marginally better fit to the data.

Table 10. Parametric model fits ranked by log likelihood (subsequent covert mortality)

Distribution	Model	LogLikelihood	Rank
Weibull	f.w	-160.085367528355	1.00
Log Logistic	f.ll	-160.274819285914	2.00
Log Normal	f.ln	-160.489825102824	3.00
Exponential	f.e	-160.950775617268	4.00
Gompertz	f.g	-160.951341749244	5.00

Next the model fit was visually assessed by fitting a semi-parametric model (Cox PH, which makes no assumptions on the underlying distribution) and plotting the cumulative hazard function the parametric and semi-parametric models for comparison. Figure 21 confirms the previous result that the Weibull model is the best approximation of the data.

Using the fitted Weibull model, the predicted survival probabilities (S_t) were calculated for use as input parameters.

4.3.4.4 Subsequent Overt (O_2) Mortality

Subsequent overt mortality was calculated as the proportion of subjects who entered any subsequent overt state that died within 30 days, namely [redacted]

[redacted]

Figure 21. Parametric and semi-parametric cumulative hazard function by distribution (subsequent covert [C_2] mortality)

4.3.5 Key results

Figure 22 illustrates the striking difference between the covert mortality models fitted to RFHE3002 data and that based on the 1999 Bustamante study[9] used in the original economic model, the former being far more clinically realistic for the subjects recruited to the OLT.

Combining the covert and overt mortality functions derived from RFHE3002 with the log-normal time to BOHE models reported in section 2.2 we observe total predicted mortality in Figure 23. Not only is predicted mortality a good visual fit to total observed mortality in the OLT but there also appears to be concordance with mortality for 'recurrent'[G] HE patients observed in UK general practice in CPRD[18].

[G] Patients surviving at least six months after first primary care Read Code record. Analysis right-censored by liver transplant (as this is assumed to dramatically reduce mortality – but is not included as a transition in the economic modelling).

Figure 22. Comparison of transitions from covert and subsequent covert states to death in RFHE3002 with Bustamante fitted model used in the original NICE submission

Figure 23. Comparison of revised modelled mortality with observed mortality from RFHE3002 patients and CPRD 'recurrent' HE patients (grey line , CPRD HE patients from 6 months after 1st HE code, censored by liver transplant; black line, 3002 mortality, all patients; green line, modelled lactulose; yellow line, modelled rifaximin)

4.3.6 Discussion

Mortality derived from the new analysis of RFHE3002 patients is compared with mortality of the CPRD HE patients who survived 6 months from diagnosis of HE along with the modelled estimates of mortality for the rifaximin and lactulose cohorts (Figure 23). The rates can also be seen in Table 11. It appears that the revised approach adopted in the model reflects the rifaximin clinical trial data and that obtained from the 6 month survivor analysis of the UK CPRD database.

Table 11. Mortality rates for studies RFHE-3001, -3002, CPRD 6 month survivors and modelled mortality for rifaximin and lactulose cohorts

Mortality	1 month	6 months	1 year	2 years	3 years	4 years	5 years
RFHE3001[3]							
Rifaximin		7.14%					
Placebo		6.92%					
RFHE3002[4]							
Overall	[redacted]	[redacted]	[redacted]	[redacted]			
Continuing RFX from 3001	[redacted]	[redacted]	[redacted]	[redacted]			
New patients	[redacted]	[redacted]	[redacted]	[redacted]			
CPRD 6 mnth survivors[18]	3.1%	14.2%	19.7%	32.8%	38.3%	43.7%	47.4%
Revised model							
Rifaximin	0.29%	6.68%	13.67%	24.95%	33.91%	41.35%	47.66%
Lactulose	0.29%	10.28%	19.11%	32.01%	41.61%	49.25%	55.53%

4.3.7 Discussion

The literature review and CPRD analysis demonstrate that mortality rate is at its highest in the first 6 month period after diagnosis with HE and that over the subsequent 6 month period the mortality rate is more in line with the mortality rates of patients in the RFHE3001 and RFHE3002 studies, who had been in remission and experienced at least one episode of overt HE in the previous 12 months before randomisation. The analysis of the mortality rates from RFHE3002 and the CPRD analysis serve as confirmation that the modelled rates more closely reflect those found in patients that have experienced and survived recurrent episodes of HE. The modelled mortality difference between rifaximin and lactulose arms that emerges after 6 months is consequence of a greater number of lactulose patients transitioning to the overt state during which they are exposed to a high 30-day mortality rate. Although a similar mortality difference did not emerge during the RCT[3], the Committee's previous clinical expert opinion[1] was such a mortality difference would be plausible.

4.3.8 Key Findings

- Time to death from the first covert state (C_1) is optimally modelled by a log-normal distribution
- 30-day mortality from the first observed BOHE (O_1) was [redacted] in RFHE3002
- Time to death from the subsequent covert state (C_2) is optimally modelled by a Weibull distribution
- 30-day mortality from the subsequent observed BOHE (O_2) was [redacted] in RFHE3002
- Combined in the economic model, predicted mortality is a close reflection not only of that observed in the open-label study but also of that observed in UK practice for survivors of the first BOHE.

5 Hepatic Encephalopathy-related Hospital Admissions

5.1 Executive Summary

The probability of hospitalisation by BOHE was incorrectly specified in the original model, leading to under-prediction of the associated costs. The difference in proportion of BOHE episodes hospitalised (favouring placebo) originally applied to the model is not statistically significant. Correcting these two deficiencies leads to an improvement of the base-case ICER of £1,200 per QALY.

5.1.1 Methods Overview

The overall rate of HE-related hospitalisation was significantly lower in the rifaximin arm than the placebo arm RFHE3001 RCT (19/140 [13.6%] vs. 36/159 [22.6%] respectively). However, in the original submission the overt state included the cost of hospital admissions caused by HE episodes. This was informed by the proportion of BOHE events that required hospitalisation within RFHE3001; 19 of 31 BOHE patients (61.29%) in the rifaximin group and 36 of 73 BOHE patients (49.32%) in the placebo group. These 6-month probabilities of hospital admission (61.29% and 49.32%) were converted to monthly probabilities of 14.63% and 10.71% respectively (assuming a constant hazard over time) and applied to the patients predicted to reach the overt state.

It has subsequently been realised that conversion from observed proportion to monthly probabilities is a category error since it dramatically under-predicts the number of HE-related hospitalisations as illustrated in Table 12. Applying the proportion of HEs hospitalised as a constant and the sample size observed in the RFHE3001 study, the model predicts hospitalisation much more closely.

Table 12. HE-related hospitalisation predicted by the original and revised economic models versus those observed in RFHE3001

	Placebo				Rifaximin			
	Cases	BOHE	HE hospitalisation		Cases	BOHE	HE hospitalisation	
Baseline	159		10.71%	49.32%	140		14.63%	61.29%
Month 1		26	2.00	12.82		8	1.17	4.90
Month 2		17	1.82	8.38		8	1.17	4.90
Month 3		12	1.28	5.92		6	0.88	3.68
Month 4		9	0.96	4.44		5	0.73	3.06
Month 5		7	0.75	3.45		4	0.59	2.45
Month 6		5	0.54	2.47		4	0.59	2.45
Predicted		76	7	37		35	5	21
Observed		73		36		31		19

The error has an appreciable effect on the cost of a BOHE, either £293/£360 for the original model (placebo & rifaximin respectively) or £950/£1,154 for the revised approach. This in turn has a small effect on the ICER; £22,056 per QALY vs. £21,416 per QALY for original and revised approaches respectively.

Of additional concern was the robustness of the difference in proportions of HE-related hospitalisations favouring the placebo group, which had not been subject to inferential statistical tests. Given the small number of events in the rifaximin arm (n=31), there would be considerable uncertainty expected around this differential.

5.1.2 Study Population

Data from the RFHE3001 study in which 19 of the 31 patients (61.29%) in the rifaximin group and 36 of the 73 patients (49.32%) in the placebo group were hospitalised because of BOHE, were applied.

5.1.3 Methods (Including Statistical Methods)

A two-tailed z-test[23] was used to compare the two observed proportions. Threshold significance was set at p=0.05.

5.1.4 Analysis

As shown in Panel 4 and Figure 24 there is considerable overlap between the 95% confidence intervals (CI) for the observed proportion of HE-related hospitalisation as a function of total observed BOHE. As p=0.263 > 0.05 the null hypothesis that there is in fact no difference between the observed proportions cannot be rejected.

z-test to compare two proportion

Analysed: Wed Sep 11, 2013 @ 22:26

Inputs

	Sample 1	Sample 2
Sample Proportion	0.6129	0.4932
Sample size	31	73
Significance level	0.05	
1- or 2-tailed test	2-tailed	

Results

	Sample 1	Sample 2	Difference
Sample proportion	0.6129	0.4932	0.1197
95% CI (asymptotic)	0.4414 - 0.7844	0.3785 - 0.6079	-0.09 - 0.3294
z-value	1.1		
P-value	0.2633		
Interpretation	Not significant, accept null hypothesis that sample proportions are equal		
n by pi	n * pi >5, test ok		

Panel 4. Post hoc comparison of HE-related hospitalisation between rifaximin and placebo treatment arms of the RFHE3001 study

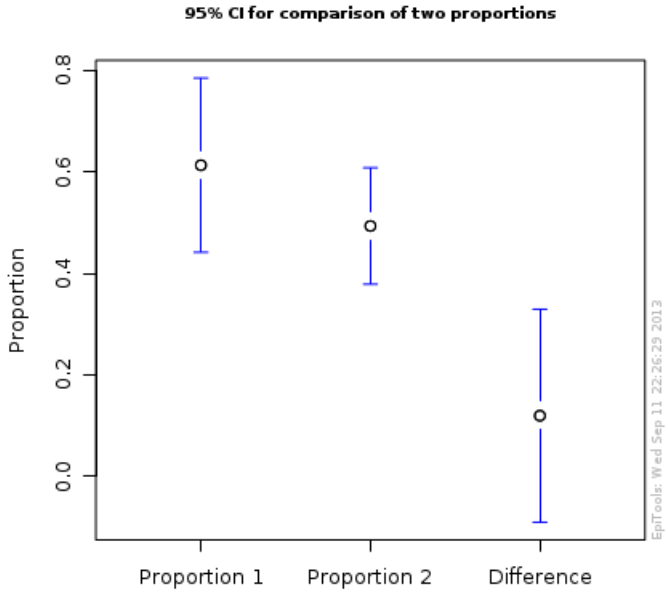


Figure 24. Confidence plot for observed proportions of HE-hospitalisation between rifaximin and placebo arms of the RFHE3001 study

5.1.5 Results Summary

This comparison of the proportions of BOHEs hospitalised in either the rifaximin or placebo group shows there is no statistically significant difference between the two treatment groups.

The aggregated proportion for all BOHEs of 52.9% is therefore a more appropriate approximation of proportion hospitalised.

5.1.6 Discussion

Having demonstrated no significant difference in proportion of BOHEs hospitalised between treatment arms in the RFHE3001 study, application of a revised aggregated proportion (52.9%) equally to both sides of the economic model yields a BOHE cost of £1,011 and an ICER of £20,799 per QALY. This represents a net reduction in £1,232 per QALY over the original model base case specification.

5.2 Key Findings

- The original model specification of monthly probability of HE-related hospitalisation significantly under-predicted the cost of hospitalisation,
- A post hoc comparison of the observed difference in the proportion of BOHE hospitalised shows no statistically significant difference between rifaximin and placebo groups in the RFHE3001 study (p=0.263),
- Applying a single revised probability of hospitalisation to the base-case model reduces the ICER by £1,232 over those originally specified.

6 Economic Modelling Results

6.1 Base-case

Following the rebalancing of the economic model of rifaximin-α 550mg for the prevention of recurrence of HE in England & Wales, undertaken following the publication of the ACD in June 2013, the following cost-effectiveness results are presented.

Rifaximin-α 550mg, when used to prevent recurrence of HE, demonstrates a cost per QALY of £20,799. This was estimated using a 5-year extrapolation of the pivotal efficacy RFHE3001 RCT with a log-normal distribution curve for both the rifaximin-α 550mg and placebo arms, each with usual standard of care.

As described above, the model distributions are varied in both the initial treatment phase and then a subsequent treatment phase. The base-case result assumes a further log-normal distribution after a patient has experienced an overt HE episode. This has been chosen as it is the best mathematical fit and better describes the subsequent C_2 to O_2 transition. It is important to note that in the original version of the model a constant exponential function was applied in this phase of the model which did not take into account the effects of prior episodes on the chance of having subsequent BOHE

6.2 Sensitivity Analysis

The following sensitivity analysis is presented to explain the potential variance in the model, and to specifically explore the use of alternative extrapolation curves both in the first and subsequent phases of treatment.

Norgine's original model (adjusted by the ERG) produced a base-case result of £22,298 per QALY, outlined in Table 13 below:

Table 13. Copied from ERG Addendum: Impact on final ICERs of using different distributions, 5-year analysis

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

[1] This ICER corresponds to the base-case value with the corrections made by the ERG (ERG Report)
[2] The ERG identified a potential mistake in one of the parameters of the Log-normal regression from RFHE3001 suggesting that this ICER might not be reliable.

Table 14 presents the results from the revised model alongside the results presented previously for comparison. It is important to note that the combined RFHE3001 and RFHE3002 analysis is no longer included; as this analysis has not been used in the new model to fit any of the mathematical extrapolations. RFHE3001, solely, has been used for the extrapolation exercise. RFHE3002 has been used to help understand the application of mathematical curve extrapolations to the subsequent BOHE and thus, this is also presented below.

Table 14. Cost per QALYs for 5 year Analysis – Original vs. Revised Model

5-year analysis	Extrapolation from RFHE3001 (Original Model)	Extrapolation from RFHE3001[a] (Revised Model)	Extrapolation from RFHE3002[b] (Revised Model)
Exponential	£20,230	£19,687	£13,779
Weibull	£20,102	£18,909	£15,830
Gompertz	£27,139	£19,504	£19,872
Log-normal	£29,038[3]	**£20,799**	[c] **£20,799**
Loglogistic	£23,164	£19,383	£21,380

a. Showing the effect of varying the survival distribution of the first BOHE transition whilst assuming a log-normal distribution for subsequent transition from covert to overt (best fit to RFHE3002 data)
b. Showing the effect of varying the survival distribution of subsequent BOHE transitions whilst assuming a log-normal distribution for first BOHE transition (best fit to RFHE3001 data).
c. The result shown in this box is the same as that for the standard extrapolation for log-normal. Log-normal distribution has been used for both the 1st and 2nd phase of the model.

These results demonstrate that the model has produced a more stable cost-effectiveness estimate than previously, particularly with regard to the choice of survival distribution for extrapolation of the primary efficacy endpoint from RFHE3001. The effect of varying the mathematical extrapolation for the 1st phase of the model, C_1 to O_1, produces a much smaller range of ICERs than previously (£18,909 - £20,799 vs. £20,102 - £29,038 respectively).

Varying the 2nd phase of the model, C_2 to O_2, does have an effect on the cost per QALY outputs, particularly the original assumption of an exponential function. Having a constant rather than declining function (a clinical expert criticism of the original model) does improve the cost-effectiveness to £13,779. Norgine believe that a log-normal distribution, which produces an ICER of £20,799, in the 2nd phase of the model is a better representation of that clinical opinion.

Importantly, if the results of moving between the log-normal and Gompertz extrapolations are examined, the effects of re-balancing the model away from over reliance on mortality towards the changed utility assumptions are demonstrated.

In the revised model, the Gompertz extrapolation produces a slightly better ICER as more patients are now surviving overall, and can therefore benefit from the improved utility conferred by rifaximin-α 550mg in the covert states. Using the previous mortality functions (derived from Bustamante[9]), used in the original submission, patients were being lost to death too quickly to accrue significant heath gain.

Table 15 shows the cost per QALY data for the 10 year analysis; original vs. the revised model. The results for the original model are the adjusted ERG produced ICERs. Norgine has repeated this 10 year analysis to test the revised model's reliance on mortality.

Table 15. Cost per QALYs for 10 year Analysis – Original vs. Revised Model

10-year analysis	Extrapolation from RFHE3001 (Original Model)	Extrapolation from RFHE3001[a] (Revised Model)	Extrapolation from RFHE3002[b] (Revised Model)
Exponential	£15,652	£22,736	£12,867
Weibull	£15,065	£21,335	£14,674
Gompertz	£21,144	£22,344	£24,581
Log-normal	[3]£21,137	£23,659	£23,659
Loglogistic	£17,212	£21,725	£25,420

3, a, b – see notes to Table 13 and Table 14

The results in Table 15 demonstrate that changing the time horizon from 5 years to 10 years has little effect on the cost per QALY in the revised version of the model; £21,335 (Weibull) to £23,659 (log-normal).

The 10 year log-normal ICER is 23,659; an increase of approximately £3,000 from the base-case 5 year log-normal ICER of £20,799. Norgine believes this demonstrates the revised model is not driven by mortality inputs. Changing the mathematical assumption curve in the second phase of the model does have an effect on the cost per QALY, as with the 5 year extrapolation.

Table 16 summarises the overall sensitivity analyses for the revised model. The ICER is relatively insensitive to the choice of survival distribution for either $Covert_1$ or $Covert_2$ mortality (£19,796 to £21,630) but is somewhat sensitive to the incremental utility of the rifaximin cohort (see Table 7 in utility section 3) in the remission state (£13,859 to £41,663 for the lower and upper bound confidence limits respectively).

Table 16. Summary of sensitivity analyses for the revised model

	60 months	120 months
Base-case	£ 20,799	£ 23,659
Covert$_1$ to Overt$_1$ survival distribution		
Exponential	£ 19,687	£ 22,736
Weibull	£ 18,909	£ 21,335
Gompertz	£ 19,504	£ 22,344
Log-logistic	£ 19,383	£ 21,725
Covert$_2$ to Overt$_2$ survival distribution		
Exponential	£ 13,779	£ 12,867
Weibull	£ 15,830	£ 14,674
Gompertz	£ 19,872	£ 24,581
Log-logistic	£ 21,380	£ 25,420
Covert$_1$ mortality survival distribution		
Exponential	£ 20,814	£ 23,988
Weibull	£ 20,894	£ 24,219
Gompertz	£ 20,455	£ 22,781
Log-logistic	£ 20,873	£ 24,011
Covert$_2$ mortality survival distribution		
Exponential	£ 19,796	£ 21,285
Gompertz	£ 20,383	£ 22,704
Log-normal	£ 21,114	£ 24,601
Log-logistic	£ 21,630	£ 25,942
Utilities		
Rifaximin LCL	£ 41,663	£ 36,929
Rifaximin UCL	£ 13,859	£ 16,687

LCL – lower confidence limit; UCL – upper confidence limit

7 Overall Conclusion

Norgine have undertaken a detailed review of the available published literature, clinical studies and there incorporation into the economic analysis for rifaximin-α 550mg. The review was based on the critique of the initial submission of evidence to the Institute as part of a Single Technology Appraisal (STA) Process.

That critique particularly focused on the original model's over reliance on rifaximin-α 550mg reducing mortality in these patients and unrealistic assumptions for utility.

Norgine's review has led to a "re-balancing" of the economic model to present rifaximin-α 550mg as a cost effective treatment for the prevention of recurrence of overt HE episodes in patients with liver cirrhosis.

Norgine found the ICER for rifaximin-α 550mg, used for its licensed indication, was £20,799. Additional sensitivity analysis was presented for a much more stable ICER, not over reliant on differential mortality. The model was re-balanced towards superior utility based on the published proven difference in patient quality of life from the RFHE3001 pivotal study.

Norgine therefore believe that rifaximin-α 550mg is both clinically effective and cost effective. The company now request that the drug should be approved for use in reducing recurrence of overt episodes of HE in liver cirrhosis patients in England & Wales.

8 References

1 NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. Appraisal consultation document Rifaximin-alpha for maintaining remission from episodes of hepatic encephalopathy. London, 2013.

2 Bass NM, Mullen KD, Sanyal A, *et al.* Rifaximin treatment in hepatic encephalopathy. *The New England Journal of Medicine* 2010; **362**: 1071–81.

3 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.

4 Salix Pharmaceuticals Inc. Clinical Study Report. A Multi-Center, Open-Label Trial to Evaluate the Long-Term Safety and Tolerability of Rifaximin 550 mg BID in Subjects with a History of Hepatic Encephalopathy (RFHE3002). Morrisville, NC, 2011.

5 Mullen KD, Sanyal AJ, Bass NM, *et al.* The Long Term Efficacy and Safety of Rifaximin in the Maintenance of Remission From Overt Hepatic Encephalopathy in Cirrhotic Patients. *GASTROENTEROLOGY* 2012; **142**: S41–S42.

6 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.

7 MHRA. The Clinical Practice Research Datalink. www.cprd.com (accessed 30 Sep2013).

8 Briggs A. Parametric survival models and decision models. Relating continuous hazards to discrete-time transition probabilities. Oxford, 2006.

9 Bustamante J, Rimola a, Ventura PJ, *et al.* Prognostic significance of hepatic encephalopathy in patients with cirrhosis. *Journal of hepatology* 1999; **30**: 890–5.

10 Norgine Ltd. A review of mortality in chronic liver cirrhosis (Appendix I). Uxbridge, 2013.

11 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.

12 Department of Health. NHS Reference Costs 2010-11. 2013.http://data.gov.uk/dataset/nhs-reference-costs-2010-11/resource/2e929335-bfe2-4257-b5d8-69bafad74821 (accessed 1 Oct2013).

13 McLernon DJ, Dillon J, Donnan PT. Health-state utilities in liver disease: a systematic review. *Medical decision making : an international journal of the Society for Medical Decision Making* 2008; **28**: 582–92.

14 Gray AM, Rivero-Arias O, Clarke PM. Estimating the association between SF-12 responses and EQ-5D utility values by response mapping. *Medical decision making : an international journal of the Society for Medical Decision Making* 2006; **26**: 18–29.

15 IBM Corp. IBM SPSS Statistics for Windows, Version 20.0. 2011.

16 Dolan P. Modeling valuations for EuroQol health states. *Medical Care* 1997; **35**: 1095–108.

17 Wells CD, Murrill WB, Arguedas MR. Comparison of Health-Related Quality of Life Preferences Between Physicians and Cirrhotic Patients: Implications for Cost–Utility Analyses in Chronic Liver Disease. *Digestive Diseases and Sciences* 2004; **49**: 453–8.

18 Pharmatelligence. An evaluation of the epidemiology and outcome of liver failure with particular focus on hepatic encephalopathy (Appendix II). Cardiff, 2013.

19 Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. *Hepatology (Baltimore, Md)* 2010; **51**: 1675–82.

20 Stewart CA, Malinchoc M, Kim WR, Kamath PS. Hepatic Encephalopathy as a Predictor of Survival in Patients With End-Stage Liver Disease. 2007; : 1366–71.

21 Neff GW, Christian M, Ramirez M. Long-term survival following overt hepatic encephalopathy. *American Journal of Gastroenterology* 2012; **107**: S606.

22 Vlachogiannakos J, Viazis N, Vasianopoulou P, Vafiadis I, Karamanolis DG, Ladas SD. Long-term administration of rifaximin improves the prognosis of patients with decompensated alcoholic cirrhosis. *Journal of gastroenterology and hepatology* 2013; **28**: 450–5.

23 EpiTools. 2-sample z-test to compare sample proportion. 2013.http://epitools.ausvet.com.au/content.php?page=z-test-2 (accessed 1 Oct2013).

9 Appendices

The following documents are supplied separately as appendices to the addendum.

Appendix I: Norgine Ltd. A review of mortality in chronic liver cirrhosis (Appendix I). Uxbridge, 2013.

Appendix II: Pharmatelligence. An evaluation of the epidemiology and outcome of liver failure with particular focus on hepatic encephalopathy (Appendix II). Cardiff, 2013.

Appendix III: Updated Literature Search

Appendix IV: Updated Budget Impact