Supplementary data

Model assumptions, data sources and outcomes

The model used clinical data, which was derived from a pivotal randomised study in which the primary endpoint was time to first breakthrough overt HE episode (RFHE3001). Time to first breakthrough OHE events is the duration from the time of first treatment, that was used in the study, to the first breakthrough OHE event. The study did not capture the length of OHE episodes because subjects discontinued at the time of breakthrough overt HE episode.

Modelling of clinical efficacy

Visual inspection of the five different fits indicates that the lognormal is the best fit to the Kaplan-Meier (KM) survival curves of time to breakthrough OHE (Figure 1, Figure 2). The estimated distribution parameters are used to measure the time-dependency transition probabilities, according to the following formula:

$$tp(t_u) = 1 - \exp\{H(t-u) - H(t)\}$$

where u is the Markov cycle and t_u indicates that t is calculated as integer multiples of the cycle length of the model (Briggs et al., 2006). $H(t)$ is a cumulative hazard function that can be calculated for lognormal distribution as following: $H(t) = -\ln\left[1 - \Phi\left(\frac{\ln(x)}{\sigma}\right)\right], x \geq 0;\ \sigma > 0$, where Φ is the cumulative distribution function of the normal distribution. The estimated log-normal model parameters are reported in Table 1. To test the proportional hazards assumption over the 6-month observation period of RFHE3001, a Cox proportional survival model was realised to test the Pearson correlation between Shoenfeld residuals. There was no significant correlation between treatment allocation and Shoenfeld residuals (p=0.1865). Therefore, there is no evidence for a violation of the proportional hazards assumption of treatment effect.

As the study endpoint in trial RFHE3001 was the first breakthrough OHE episode, there are no data for subsequent OHE events for both trial arms. With the purpose of estimating the survival curve for time to subsequent OHE, the assumption was made that RFHE3001 and RFHE3002 should be comparable in time to subsequent OHE events.

Therefore, modelling of time to subsequent observed OHE was conducted using data from the open-label RFHE3002 (OLT) study using all OHE events excluding the first observed OHE event. Based on the findings of analysis that the RCT and OLT were comparable in terms of time to first observed OHE, the assumption was made that they should also be comparable in time to subsequent OHE events had RFHE3001 'event-failures' been further followed. In this analysis, only new rifaximin-α treated subjects from the RFHE3002 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 to the rifaximin-α] treated subjects in the RCT in terms of time to first OHE (log-rank p=0.268) and also because this would isolate the results from any potential enrichment bias, resulting from inclusion of event-free survivors from the RCT.

A survival analysis was performed to compare OHE event rates following first observed OHE event within the clinical trials compared with subsequent observed OHE events. This analysis was required for consistency with the economic model that reflects different event rates based on previous OHE events. The survival analysis demonstrates that event rates differ depending on whether experiencing first OHE or subsequent OHE event. The survival curves were used to populate survival rates in the economic model.

Subsequent to generating the survival curves, an independent assessment of which distribution best fits the time to subsequent OHE event in the RFHE3002 data using only the newly recruited subjects. Five parametric survival models were fitted to the pooled time to subsequent event data from the new rifaximin-α-naïve patients recruited to the RFHE3002

study, one for each candidate distribution. The goodness of fit of the models to the data was assessed both statistically (Table 2) and graphically using the same criteria as for time to first breakthrough episode. The log-normal distribution appears to offer the optimal fit to the RFHE3002 subsequent HE event data.

Unadjusted KM survival curves visually indicated that the time to event decreases with increasing of event cardinality. To generate the survival curves, an independent assessment was applied to find the most suitable distribution for the time to subsequent OHE event based on the RFHE3002 data, which used only newly recruited subjects. Five parametric survival models have been adjusted to the time to subsequent event data derived from the new rifaximin-α-naïve patients, who were recruited in the RFHE3002 study. The log-normal distribution appears to offer the optimal fit to the RFHE3002 subsequent OHE event data which is based on the suitability of fit of the models to the data. This conclusion was obtained using both statistical and visual criteria (Table 2, Figure 3). Based on the treatment effect proportionality assumptions and the durability at different stages of patients' disease history, the model takes the inverse of the rifaximin-α estimated parameter, which have been used in the first transition model, and applies it equally to the lognormal parametric survival model for pooled subsequent events. The lactulose survival curve was obtained by multiplying the curve of rifaximin-α by the corresponding hazard ratio.

According to the opinion of expert very few overt HE episodes have a duration exceeding 30 days. Additionally, they suggested that all patients, who do not die during an overt HE cycle, are assumed to recover fully into the subsequent covert (CHE2) state.

The model uses overall mortality, which has been not only observed in the RFHE3002 study but also in the one reported in literature (Bustamante et al., 1999), in the study of Toulouse University Hospital and French clinical practice.

All-cause mortality

The cost-effectiveness model adjusts for all-cause mortality based on published French life tables (Chautant, 2013). The original age of the cohort considered in the analyses was 62 years. The risk is adjusted to incorporate the weighted average of the ratio of males to females in the RFHE3001 study (60.9% and 39.1% of the ITT population were male and female, respectively). Given the relatively small contribution of deaths from liver disease to the total population mortality burden, deaths due to liver disease or HE-related deaths are not disaggregated from all-cause mortality. However, the inclusion of all-cause mortality can be disabled in the version of the model submitted with the economic evaluation.

Disease-specific mortality

There is evidence to suggest that patients who experience OHE events face a higher mortality risk than patients without HE, the mortality risk increases further with more severe grade of HE (Bustamante et al., 1999; Shawcross et al., 2011). Mortality data from RFHE3001 were not sufficiently mature to address the impact of rifaximin-α on survival. Therefore, data from the open-label clinical study RFHE3002 was used to model four mortality functions consistent with the health states specified by the economic model. Whilst there were sufficient subsequent HE episodes (n=102) in RFHE3002 new patients to calculate parametric survival models for time to subsequent overt HE, there were far fewer deaths in this subgroup to inform survival modelling. It was decided to pool all patient subsets from RFHE3002 for the purposes of modelling disease-specific mortality. The similar outcomes among the rollover and crossover patients was first compared to the new patients recruited to RFHE3002 by examining time to first HE in the study. Log rank tests of difference in survival curves for new subjects and for subjects recruited from RFHE3001 suggest that event-free survival between the subgroups was not statistically significantly different (p=0.893 and p=0.643 for new vs. rifaximin-α and new vs. PLB respectively). Time to death from the covert states

(CHE1 and CHE2) was analysed using parametric proportional hazards survival modelling. 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 HE (OHE1) and then similarly for combined subsequent HE events (OHE2).

Five parametric survival models were fitted to the OLT data, one for each candidate distribution. The log normal distribution appears to offer the best fit the survival distribution for covert mortality (Figure 4).

Modelling of the time to death in the subsequent covert state (CHE2) was achieved using parametric survival modelling for the combined subsequent covert state dataset from study RFHE3002, analogous to that used to model time to subsequent HE. The Weibull distribution appears to offer a marginally better fit the subsequent covert mortality (Figure 4).

As no single overt episode is assumed to last more than 30 days (equivalent to one model cycle) survival modelling whilst in the overt state (either first-observed or subsequent) is not warranted. To derive the likelihood of mortality within 30 days of an overt HE event, the probability of death was derived from observed death rates following the first-observed overt HE state. This was calculated to be 11.1%. The probability of death in a subsequent overt HE state ≥O2 was calculated as the number of subjects who died within 30 days of entering any subsequent overt HE state (n=15) in study RFHE3002 divided by the total number of subsequent overt episodes (n=194). This was calculated to be 7.7%.

Valorisation of health states

Health state utilities have been derived for the overt and covert health states in the model. An utility study was performed by Norgine using Time Trade-off or TTO (Norgine Ltd., 2013). Utility values (ranging from 1.0 for a perfect health to 0 for a death) were obtained for five

different health states. T-test was applied to evaluate statistical significance between different groups.

Utility in the covert state was derived using the published results from post hoc analysis of the RFHE3001 (Sanyal et al., 2011). That data showed that in the covert remission state the rifaximin-α treated patients experienced an incremental improvement in QoL as measured by the Chronic Liver Disease Questionnaire (CLDQ) over those receiving placebo. At first, a relationship was derived between EQ-5D questionnaire and disease-specific questionnaire CLDQ. Then, the conversion of SF-36 data into EQ-5D utilities was performed using the response mapping algorithm developed by Gray et al (Gray et al., 2006). 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. Exploratory analysis of the relationship between 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. The cubic or quadratic functions have the highest explanatory power ($R^2 = 0.590$), and the linear function is only marginally lower with 58.7% of variation in EQ-5D utility explained by CLDQ score.

Net monetary benefit

In the present model the net monetary benefit (NMB) approach was used as an alternative of using the incremental cost-effectiveness ratio (ICER). NB method allows to avoid the limitations of ICER approach (A. H. Briggs et al., 2002). Net Benefit can be expressed in health (NHB) or monetary (NMB) terms. The intervention with the higher Expected Net Benefit is the cost effective choice.

$$NHB_i = E_i - \frac{C_i}{\lambda}$$

$$NMB_i = E_i * \lambda - C_i$$

where C_i is the cost under the intervention of interest, E_i is the effectiveness the intervention of interest, and λ is the cost effectiveness threshold/willingness to pay for health. The intervention with the higher positive NMB is a preferred treatment. The probability that the new technology is cost-effective comparing to the current technology is calculated in four steps:

- compare the NMB for each simulation run;
- count the cases when new technology has the greater NMB;
- divide this number by the total number of simulations.

A cost-effectiveness acceptability curve or CEAC is a graphical representation of the quantitative measure of uncertainty around the expected cost effectiveness. However, CEAC does not tell the decision maker that technology has the highest Expected Net Benefit, and this is the criterion that we expect decision makers will use when selecting a cost effective option (A. H. Briggs et al., 2002). The choice facing decision makers is to maximise Expected Net Benefit for a relevant value of lambda. The cost-effectiveness acceptability frontier (CEAF) is constructed by plotting the CEACs for the technologies being compared. And then the technology with the highest Expected Net Benefit at each value of lambda and for each CEAC trace the portion where the technology also has the highest Expected Net Benefit was identified. To calculate the point where the frontier 'switches', the point of the same net monetary benefit for two options was used:

$$\overline{NMB_2} = \overline{NMB_1}$$

$$\overline{E_2} * \lambda^* - \overline{C_2} = \overline{E_1} * \lambda^* - \overline{C_1}$$

$$\lambda^* = \frac{\overline{C_2} - \overline{C_1}}{\overline{E_2} - \overline{E_1}} = ICER$$

References

Briggs, A.H., Goeree, R., Blackhouse, G., O'Brien, B.J., 2002. Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. Med Decis Mak. 22, 290–308.

Briggs, A., Sculpher, M., Claxton, K., 2006. Decision Modelling for Health Economic Evaluation, 1 edition. ed. OUP Oxford.

Bustamante, J., Rimola, A., Ventura, P.J., Navasa, M., Cirera, I., Reggiardo, V., Rodés, J., 1999. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. J. Hepatol. 30, 890–895.

Chautant, F., 2013. Evaluation de l'utilisation de la rifaximine dans la prise en charge de l'encéphalopathie hépatique du patient cirrhotique au CHU de Toulouse.

Gray, A.M., Rivero-Arias, O., Clarke, P.M., 2006. Estimating the association between SF-12 responses and EQ-5D utility values by response mapping. Med. Decis. Mak. Int. J. Soc. Med. Decis. Mak. 26, 18–29. doi:10.1177/0272989X05284108

Norgine Ltd., 2013. (Data on file) Utility values for specific hepatic encephalopathy health states elicited from the general public in the.

Sanyal, A., Younossi, Z.M., Bass, N.M., Mullen, K.D., Poordad, F., Brown, R.S., Vemuru, R.P., Mazen Jamal, M., Huang, S., Merchant, K., Bortey, E., Forbes, W.P., 2011. Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy - a double-blind placebo-controlled study. Aliment. Pharmacol. Ther. 34, 853–861. doi:10.1111/j.1365-2036.2011.04808.x

Shawcross, D.L., Sharifi, Y., Canavan, J.B., Yeoman, A.D., Abeles, R.D., Taylor, N.J., Auzinger, G., Bernal, W., Wendon, J.A., 2011. Infection and systemic inflammation, not ammonia, are associated with Grade 3/4 hepatic encephalopathy, but not mortality in cirrhosis. J. Hepatol. 54, 640–649. doi:10.1016/j.jhep.2010.07.045

***Table 1**. Estimated parameters for log-normal parametric survival model of time to first OHE episode in study RFHE3001.*

	Coefficient value	S. E.	P-value	lower CI	upper CI
Rifaximin-α*	1.094	0.269	<0.001	0.568	1.621
Constant†	1.796	0.177	<0.001	1.450	2.142
Ln(sigma)‡	0.624	0.0763	<0.001	0.474	0.773

S.E.: Standard Error; lower CI, upper CI: 95% confident interval;
*: rifaximin-α treatment arm; †: constant component; ‡: natural logarithm of sigma coefficient.

***Table 2.** Model fit statistics for alternative candidate parametric survival distributions, time to subsequent breakthrough overt episode (RFHE3002 new subjects) (Extract from the report Norgine, Belgium).*

Model	**Log Likelihood**	**AIC**	**BIC**
Exponential	-388.57	777.14	777.14
Weibull	-381.78	763.57	763.57
Gompertz	-377.56	755.11	755.11
Log-Normal	**-377.20**	**754.40**	**754.40**
Log-Logistic	-377.80	755.60	755.60

AIC: Akaike information criterio; BIC: Bayesian information criterion.

***Table 3.** Parameter estimates for lognormal parametric survival model of time to subsequent overt HE episode in study RFHE3002 (new patients) including treatment effect from event-free survival model (Extract from the report Norgine, Belgium).*

	Coefficient	**Std. Err.**	**P-value**	**lower CI**	**upper CI**
Lactulose*	-1.0944	0.2686	0.0000	-1.6210	-0.5679
Constant†	1.3830	0.1993	0.0000	0.9924	1.7736
Ln(sigma)‡	0.5533	0.0942	0.0000	0.3686	0.7380

S.E.: Standard Error; lower CI, upper CI: 95% confident interval;
*: lactulose treatment arm; †: constant component; ‡: logarithm of sigma coefficient.

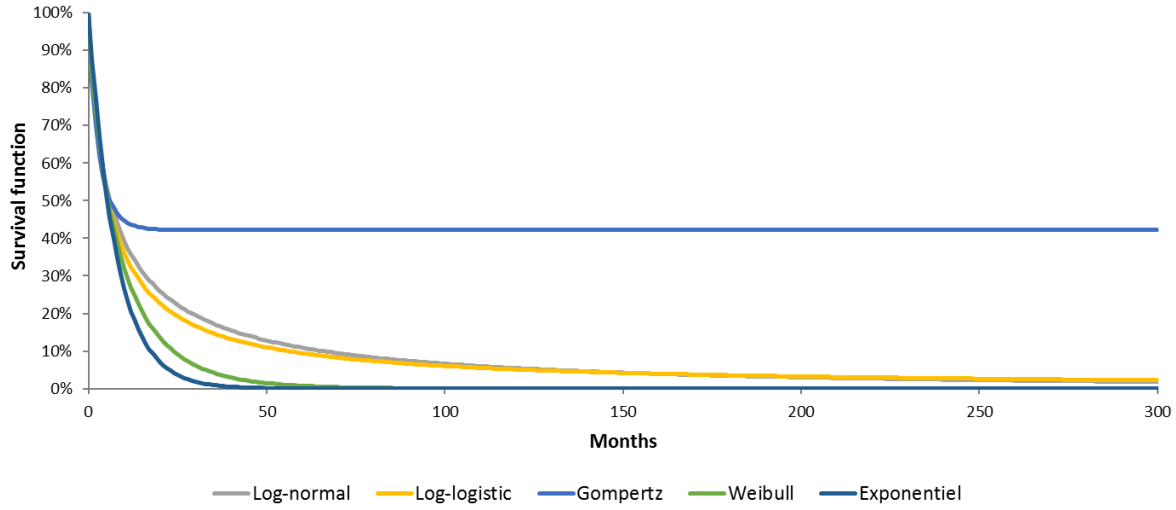

Figure 1. *Comparison of five resulting parametric event-free survival distributions for time to first overt HE event for lactulose arm in the RFHE3001 study.*

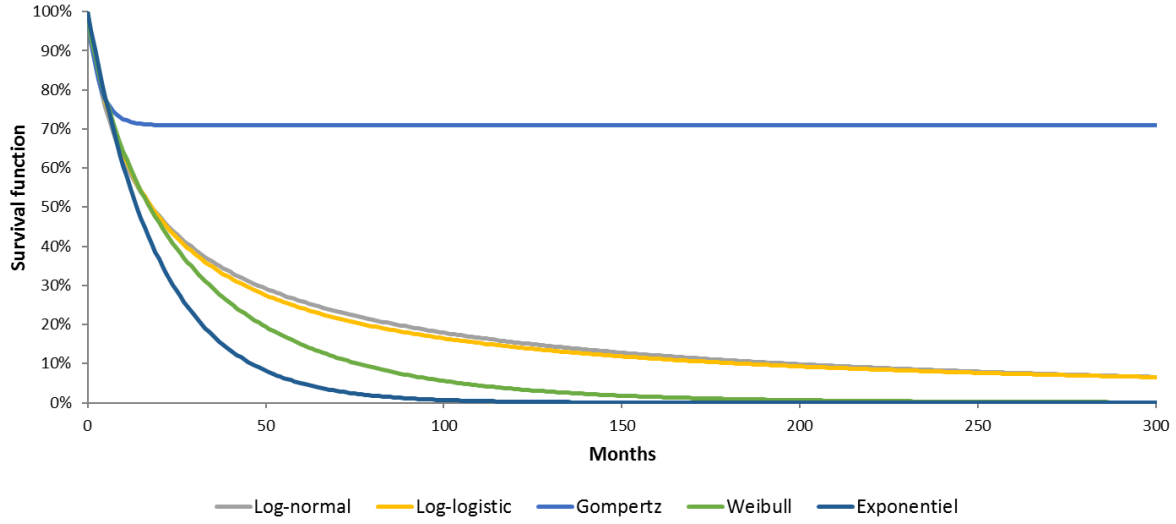

Figure 2. *Comparison of five resulting parametric event-free survival distributions for time to first overt HE event for rifaximin-α arm in the RFHE3001 study.*

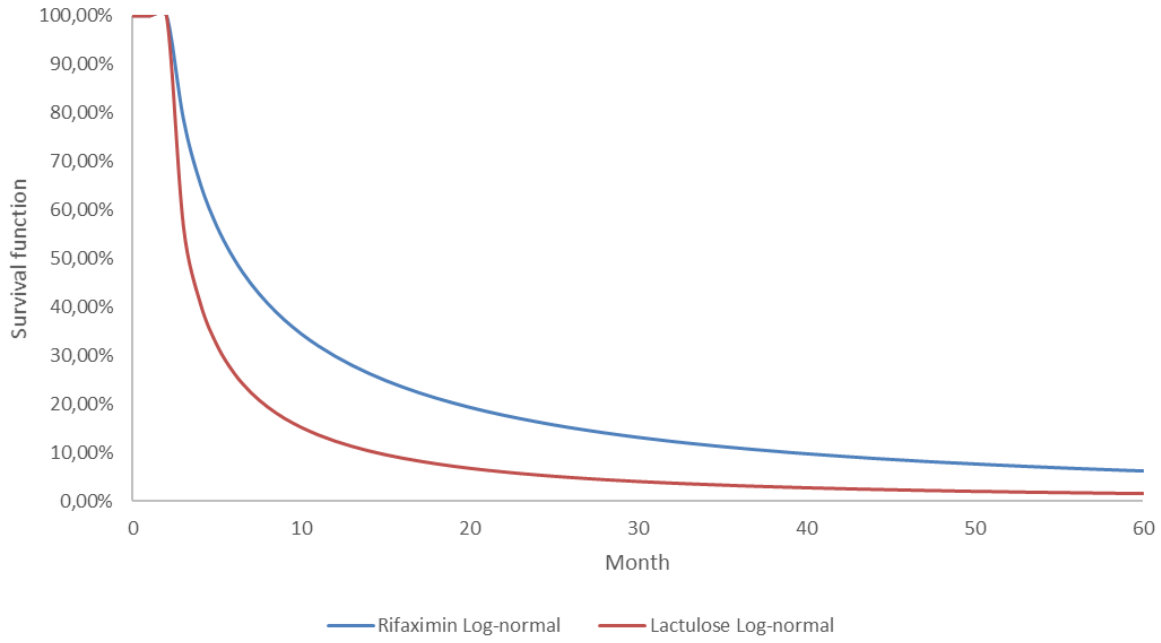

Figure 3. *Best-fit parametric survival function (log-normal) for time to subsequent overt HE event in the RFHE3002 study with fitted lactulose arm based on the inverse treatment effect modelled from time to first event data in study RFHE3001.*

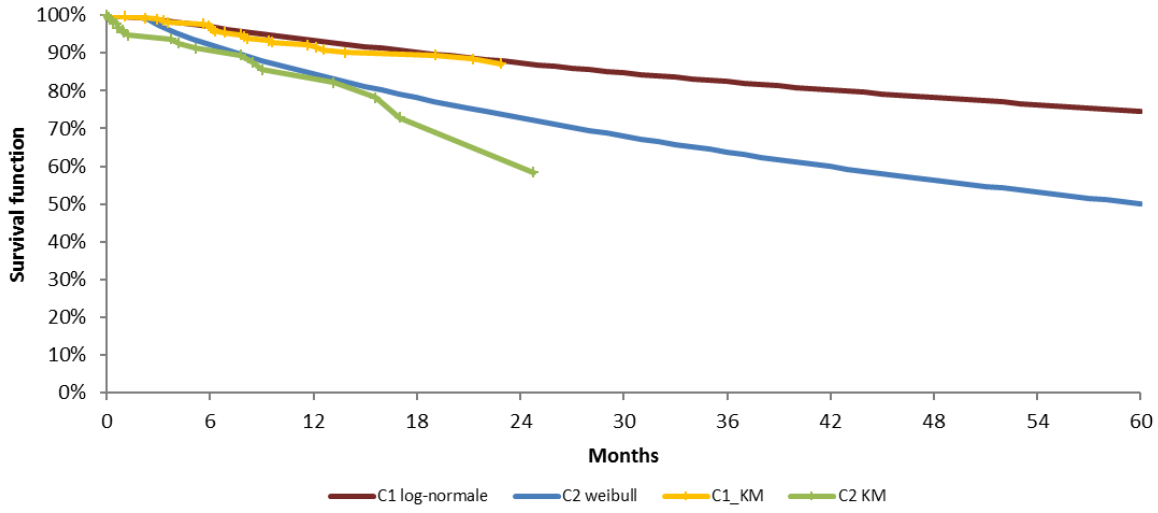

Figure 4. *Comparison of mortality curves and their best adjustments parametric curves (log-normal for CHE1 and Weibull for CHE2).*