Further Submission NICE STA: Hepatic encephalopathy - rifaximin (maintenance) [ID496]

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Executive Summary

Introduction

Following a third Committee meeting in April 2014 (and the drafting of a Final Appraisal Determination in May 2014) the Institute has agreed that the STA process **Hepatic encephalopathy - rifaximin (maintenance) [ID496]** is still not complete.

Consequently the FAD remains unpublished and the appraisal will be taken back to the Committee for further consideration of the evidence. This is a further submission of supportive data for consideration by the Appraisal Committee.

Norgine outlines four key areas of additional input to the Committee for consideration:

1. **The use of minimum important difference (MID) data to support the assumption of utility gain in patients with covert hepatic encephalopathy (HE) treated with rifaximin-α.**
   The Committee has not previously accepted the impact of the higher level of health related quality of life from rifaximin-α therapy in HE patients who are in the covert HE state in between recurrent overt HE episodes. A range of MID inputs are used to support the assumption that this higher level is more appropriate and is consistent with feedback from both physicians and representatives of patients and carers. A recent study [1] reported improvements in Quality of Life substantially greater than the 10% seen in the pivotal clinical trial [2, 3]

2. **The application of the results of a series UK "real world" data audits in the economic modelling for rifaximin-α.**
   The impact on both reduction in hospitalisations and length of inpatient stay seen when treating HE patients in the UK with rifaximin-α is included in the economic analysis for this healthcare intervention. This analysis shows that rifaximin-α is at the very least cost-effective if not cost saving when used as part of routine care for patients with recurrent overt HE in the UK.

3. **An analysis of the effects of NHS policy in England & Wales on reducing hospital bed stay.**
   An analysis of hospital episode statistic data showing that the programs introduced in NHS England & Wales to increase efficiency and reduce hospital bed stay had no effect on the hepatology clinical specialty during the period of the real world audits

4. **Further data to support the long term effectiveness of rifaximin-α, and its effect on mortality.**
   Rifaximin-α has long term data to support its clinical use beyond 6 months to

reduce recurrence of overt episodes and has the potential to have a positive effect on the mortality of HE patients.

Executive Summary - Background

Hepatic encephalopathy (HE) is a condition, associated with liver disease, which results in what is essentially a delirious state, fluctuating between a covert and overt state but never completely abating. Thus reporting of data in these relatively uncommon patients (designated an orphan disease in the USA and certain other countries) is not straightforward. This is particularly true of Patient Related Outcome measures such as health-related utility.

Importantly, the estimated ICER for rifaximin-α plus SOC versus SOC alone (lactulose) has rested on a difference in health-related utility, in a covert HE state, described incorrectly in the unpublished FAD (May 2014) as a 'remission state'. The conclusions of the last Committee meeting (contained in the unpublished FAD, May 2014) rested mainly on the uncertainty of this issue.

The four key areas of analysis outlined should address the uncertainties expressed in the unpublished FAD.

1. **The use of minimum important difference (MID) to support the assumption of utility gain in patients with covert HE treated with rifaximin-α.**

Norgine derived the difference in utility in the covert state between the rifaximin-α cohort and standard of care cohort in two ways from a single, randomised clinical trial. Again it should be noted that it is difficult to collect RCT data in these types of patients for the reasons stated above. First with a positive utility increment of 0.106, derived from a relationship between EQ-5D and the disease specific measure (CLDQ) and second, as requested by the Committee at the second TAC (October 2013), derived directly from SF-36 converted to EQ-5D utilities, recorded in some of the patients in the trial at 0.032 units.

If this second value of 0.032, derived as requested by the Committee, is accepted, then the rifaximin-α would be regarded as cost effective. The evidence supporting this thesis is persuasive and is clearly at odds with the Committee's conclusions in the unpublished FAD.

For a clinician or patient to detect or observe an improvement in utility it would have to exceed the minimally important difference (MID) threshold, which is at least 0.03 units. There is evidence from a number of sources that the minimal important difference in EQ-5D is much higher than 0.03 (Walters and Brazier 2005 [4] posit 0.074, Pickard et al 2007 [5] suggest a higher value of 0.10 – 0.12). A recent review (Coretti et al 2014 [6]) found a range of values between 0.03 and 0.52. These authors stated that the paper by Walters and Brazier [4] was considered a benchmark. As the QoL improvements are observed and detected by both patients and physicians a value of 0.032 would appear conservative in the light of these publications.

Consideration of the effects that applying these assumptions from publications of MID are shown in Table 1.

Table 1. Outputs of Cost Effectiveness Model for Rifaximin-α in HE Patients: Incremental Cost Effectiveness Ratios at 5, 10 and Lifetime Horizon Considering the MID Utility Assumption

Covert Utility Assumption	Covert Utility Benefit	5 Year ICER	10 Year ICER	Lifetime ICER
Norgine Basecase	0.106	£20,702	£19,241	£17,810
Walters and Brazier [4] (MID estimation)	0.074	£25,907	£23,549	£21,331
Direct SF 36/EQ 5D Derived (TAC requested)	0.032	£38,669	£33,349	£28,805

The Committee believed that the most realistic assumption for utility in the economic model for rifaximin-α was derived from direct translation of the SF-36 data collected in the study. Norgine has consistently recommended that the best assumption for utility should be based on the disease specific HRQoL tool CLDQ as this more accurately reflects the impact rifaximin-α has on the patients. Sanyal et al 2011 [3] clearly demonstrated this impact. Significant improvements in QoI associated with rifaximin-α treatment have also been reported in other studies (Sidhu et al 2011 [1]; Bajaj et al 2011 [7])

The Committee acknowledged that a utility benefit with rifaximin-α **was** plausible, however the Committee was concerned by the uncertainty around the utility values in the model and the magnitude of the utility benefit used in the Norgine basecase has not been accepted by the Committee.

Norgine has repeatedly made the case that HRQoL is difficult to record in a cognitively impaired patient and the Committee accepted that rifaximin-α would have an effect on quality of life in the covert state. Thus the Company recommend that a published reference case for the utility assumption should be used. If the Walters and Brazier [4] minimally important difference for utility is assumed for this model, then rifaximin-α could be considered cost effective under a £30,000 threshold level. This should address the Committee's uncertainty over this utility assumption in the model

2. The application of the results of a series UK "real world" data audits in the economic modelling for TARGAXAN 550mg

Using data from the real-world audits, published independently by four UK centres with experience in using rifaximin-α, a model scenario was created that best simulates the resource use observed in the real-world.

As the model is based on the covert HE cohort recruited to the randomised study RFHE3001—with lower event frequency than the patients treated in routine practice—it was not possible to replicate the annualised hospitalisations rate per patient observed in the pre-rifaximin-α cohort (synonymous with standard of care),

even with 100% probability of hospitalisation on presentation of overt episode (RWD, 2.8 admissions per patient per year; Model, 1.1).

In an exploratory scenario analysis[1], to simulate observed descriptive changes in annualised inpatient bed occupancy (27.7 days per patient per annum (pppa) for standard of care vs. 8.1 days pppa for rifaximin-α), the length of stay inputs were set to 25.1 days in the standard care arm, and 14.1 days for rifaximin-α. This produces a reduction of 48% for admissions per patient per year and a reduction of 71% for annual bed occupancy in the first 12 months of treatment with rifaximin-α.

Table 2 describes the results of the model outputs adjusted to observations from Norgine's meta-analysis of the real world data audits. Under all scenarios rifaximin-α dominates standard of care in the first four years of treatment. Thereafter only the more pessimistic scenarios and longer time horizons increase the ICER above £20,000. It should be further noted that the modelling scenario described, conservatively applied the same duration of overt disutility as previously submitted (11 days based on expert clinical opinion).

Table 2 Outputs of Cost Effectiveness Model for Rifaximin-α in HE Patients: Incremental Cost Effectiveness Ratios at 5, 10 and Lifetime Horizon Considering the Effects of the Hospital Bed Stay Reduction and Reduced Hospitalizations from the RWD Audits in the UK NHS

Covert Utility Assumption	Covert Utility Benefit	5 Year ICER	10 Year ICER	Lifetime ICER
Norgine Basecase	0.106	Dominant	£4,466	£7,205
Walters and Brazier [4] (MID estimation)	0.074	Dominant	£5,465	£8,630
Direct SF 36/EQ 5D Derived (TAC requested)	0.032	Dominant	£7,740	£11,654

Baseline bed occupancy 33.8 days per patient per year (weighted mean for standard-of-care from 4 UK centres prior to introduction of rifaximin-α into clinical practice).

Following the application of the annualised resource reductions demonstrated in the real world data audits to the economic model, (represented in table 2), it is clear that rifaximin-α can be considered a highly cost effective option for the NHS in England & Wales. The current model demonstrates dominance at 5 years and high levels of cost effectiveness at the 10 year and lifetime horizon.

3. An analysis of the effects of NHS policy in England & Wales on reducing hospital bed stay

Data from hospital episode statistics (HES) taken for the period of 2011 to 2013 (the period associated with the hospital audit data) has not shown any meaningful reductions in overall hospital bed stay in the hepatology speciality. This is supported by feedback from hepatology centres in England and Wales who have confirmed that

[1] Presented to NICE prior to the suspension of the FAD

the introduction of daily ward rounds designed to reduce bed stay in their hospitals was introduced in 2009/10, which is before the periods of audit.

Guidance from NHS England focused on targeting areas where length of stay was considered too long. Feedback from hepatology specialist centres indicated that they were not considered as target areas for hospital bed stay reduction.

(see Appendix A Hospital Episode Statistics, 2010-11, 2011-12, 2012-13)

4. Long term effect and effect on mortality of rifaximin-α

4.a Further data to support the long term effectiveness of rifaximin-α.

The long-term effectiveness of rifaximin-α in reducing the recurrence of episodes of overt HE has been shown in the RFHE 3002 open label study (Mullen et al 2014) [8]. This demonstrated a sustained effect over time, which has been supported by real world data audits previously presented to the Committee. Two of these audits, Bristol and Newcastle, followed patients for longer than 6 months. A recent publication from Portsmouth confirmed the continued efficacy of rifaximin-α beyond 6 months.

The results of these studies showed a consistent reduction in hospitalisations for longer than 6 months for these patients.

Long-term efficacy of rifaximin-α is also supported by publications from other countries where follow-up has been up to 5 years (Vlachogiannakos et al 2013 [9], Neff et al 2012 [10]. Follow-up periods of greater than 6 months have also been reported from a number of international centres Confer et al [11]; Hanouneh et al [12]; Irimia et al [13]

4.b Effect on mortality of treatment with rifaximin-α

In the previous submissions data from RFHE3002 was used to model mortality. (The methods and data synthesis are described in “Addendum to Norgine NICE STA Submission on Rifaximin-α 550mg: Further Analyses in Response to Technology Appraisal Committee’s Critique of the Economic Case” submitted to NICE October 2013**.** A review of mortality in HE was submitted as an Appendix at that time.)

The AC accepted a reduction in mortality in patients with HE treated with rifaximin-α was plausible but found the magnitude uncertain. Mortality in both overt and covert states was the same in both cohorts, however, as rifaximin-α treated patients experienced fewer overt episodes, mortality was less than in the SOC cohort.

The reduction in mortality seen in the model is supported by a number of recent publications. In an RCT in patients with overt HE that compared rifaximin-α plus lactulose versus placebo plus lactulose, rifaximin-α treated patients had significantly lower mortality (23.8 % vs. 49.1 %, $P < 0.05$) [14]. It is important to note that this differential effect on mortality has not been included in the model where mortality in the overt state is the same for both cohorts

A long-term open label study also reported lower mortality compared with a matched cohort with 5-year survival probability was higher in patients receiving rifaximin-α than in controls (61% vs 13.5%, $P = 0.012$) [9].

A retrospective chart review has also reported reduced mortality in patients treated with rifaximin-α than patients treated with lactulose [10]. A recent meta-analysis of RCTs that included treatment of acute HE, covert HE and prevention of recurrence of HE concluded that treatment with rifaximin-α was associated with reduced mortality (RR: 0.64, 95% CI: 0.43– 0.94; [15].

These data support the plausibility of the modelled mortality benefit and indicate that and magnitude is not unreasonable.

Executive Summary - Conclusions

The Appraisal Committee has described a high level of uncertainty in the assumptions for HRQoL derivation and the length of effect of rifaximin-α. This has led to the decision in the unpublished FAD (May 2014) not to recommend this technology.

Norgine has outlined four key areas of evidence that support both the clinical and economic case for rifaximin-α.

- The Committee has accepted that rifaximin-α has a positive effect on quality of life in the covert state. Taking a standard benchmark of MID as a utility assumption. rifaximin-α is seen to be cost effective.
- If the cost reductions and resource efficiencies from RWD studies in undertaken in NHS England & Wales (during a period when no other clear reductions in length of stay were occurring) are applied to the economic case, rifaximin-α is highly cost effective, if not dominant in most scenarios.
- There is clear evidence to support the longer term effectiveness of rifaximin-α for reducing the recurrence of overt hepatic encephalopathy.
- The assumptions of mortality benefit used in the economic model are plausible.

Executive Summary References

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Background to this submission.

Norgine first submitted a dossier to inform the NICE STA process **Hepatic encephalopathy - rifaximin (maintenance) [ID496]** in February 2013. This clinical, health economic and budget impact case for the use of this intervention for reducing the recurrence of overt episodes of hepatic encephalopathy (HE) has been through three NICE Appraisal Committee reviews.

During this process a number of model assumptions have been variously proposed by Norgine, the Evidence Review Group (ERG) and by the Appraisal Committee (AC) as set out in the Appraisal Consultation Documents [ACD] and the Final, (unpublished), Appraisal Document [FAD] from May 2014.

In the unpublished FAD (May 2014) the Committee acknowledged that a utility benefit with rifaximin-α **was** plausible given the unanimous agreement of clinical experts and patient representatives confirming both the subjective and objective discernable impact on patient function and overall quality of life in both the overt and covert states of HE.

However the Committee was concerned by the uncertainty around the utility values in the model, given the paucity of QoI data in the overt and covert states of HE. These concerns were specifically:

- that the utility value (derived from both CLDQ-& SF36 datasets) used in the economic model in the covert state (0.106) to generate the Norgine base case was an overestimate [Section 4.12].
- that the utility difference between the covert and the overt state was likely to be underestimated [Section 4.12].

Following a request from the Committee after the second TAC meeting (October 2013) Norgine used SF-36 data only mapped directly to EQ5D to derive a utility value of 0.032. It should be noted that the SF-36 dataset had a higher proportion of missing data than the CLDQ dataset. The Committee concluded that although the utility estimates had captured the reduced quality of life associated with hepatic encephalopathy [Section 4.13], it further concluded that the increment could be lower than the maximum point estimate of 0.032 presented by the manufacturer and could plausibly decrease further during long-term treatment [Section 4.14].

Additionally "…the Committee concluded that although a mortality benefit had not been observed in RFHE3001, it was willing to accept that an initial mortality benefit with rifaximin resulting from a reduction in overt hepatic encephalopathy episodes was plausible. However, it concluded that the magnitude of the effect is uncertain, and that the most plausible mortality assumption would be between the manufacturer's base case and the extreme scenario in which there was no mortality benefit associated with rifaximin." [Section 4.16]

The Company highlighted that the Committee had not considered the following evidence as part of their review process:

1. Minimal important difference published evidence to support the acceptance of a significant improvement in covert state hepatic encephalopathy quality of life in TARGAXAN® 550mg (rifaximin-α) treated patients

2. Independent UK 'real world' audit data (including historical controls) evaluating the 12 month effectiveness of rifaximin-α for reducing the recurrence of overt episodes of hepatic encephalopathy.

Critically, the impact of these two areas on the ICER in the economic model had not been fully evaluated.

The Company also highlighted the misunderstanding of the clinical opinion supplied to the Committee and misinterpretation of other real world data supplied to the Committee by specialist hepatologists relating to the expected duration of the therapeutic effect of rifaximin-α.

The Institute accepted these arguments and suspended publication of the FAD. The Institute has agreed to a further review of the available evidence.

Rationale for This Submission

In September 2014 the NICE Guidance Executive accepted Norgine's assertion that the review of rifaximin-α was incomplete

Given the lack of reliable QoL estimates from the clinical trial it was felt that proper consideration should be given to the issue of utility based on the concept of minimal important difference (MID).

In addition full consideration of the real world audit data (presented in previous submissions) and its potential impact on the actual cost effectiveness of rifaximin-α when used in the NHS should be considered.

To address other questions raised by the Committee an analysis of Hospital Episode Statistics covering the same period as the audits is included along with evidence to support the long term effectiveness of rifaximin-α and arguments to support the mortality assumptions used in the economic model.

1. Estimation of utility value

As outlined in the unpublished FAD, the Committee considered there was too much uncertainty in relation to the assumptions taken in the calculation of utilities applied in the economic model to justify approval. However the Committee **did** accept that rifaximin-α would have clinically significant impact on quality of life in patients while they were in the covert HE state (i.e. between overt episodes of HE).

Given that there is widespread consensus by liver experts that a **detectable** clinical difference occurs in patients treated with rifaximin-α in both overt and covert states, there must be at least a minimal important difference (MID) in the utility score.

To determine the most plausible utility benefit to use in the economic model a range of publications for the assumption of minimal important difference in quality of life were reviewed.

From this review average minimal important differences (MID) were applied to the model. This demonstrates that the Company's contention that the quality of life impact of 0.106 (on a 0 to 1 utility scale) is more appropriate than the Committee's assumption of little or no utility impact. Norgine has thus applied the MID published assumptions to the model to demonstrate this impact on cost effectiveness.

2. Real world data

To complete this STA the Institute has indicated that it believes the Appraisal Committee should consider the impact of resource reduction on NHS services from the real world data audits conducted independently by a number of hepatologists in the UK following the introduction of rifaximin-α.

The first of these audits was presented to the Committee in the first submission from Norgine. Subsequent similar historical cohort audits of rifaximin-α use were presented at subsequent meetings. However, at the request of the Committee, Norgine adhered to the standard NICE reference case approach used in previous submissions. The ERG also did not use findings from these audits in its economic modelling during its review of the submission (December 2013-April 2014). This meant that, critically, no data from any of these audits was specifically applied in the core economic modelling concept. The Institute subsequently requested that the resource reductions seen in these independent real world data for consideration by the Committee. This has now been completed as requested.

3. Analysis of hospital bed stay

At the third Committee meeting, a comment was made in relation to the credibility of the real world data audits. Specifically that the resource reductions demonstrated in these audits may have been a consequence of increased efficiencies in NHS care driven by recent focus on targets to reduce hospital bed stay, and not attributable to the use of rifaximin-α for reduction of recurrence of overt HE.

Using Hospital Episode Statistics (HES data) the Company has investigated this issue further. It appears that any changes to NHS policy that may have driven a reduction in admissions and bed stays occurred **before** the audits commenced and so would not have affected the findings of the audits. Furthermore, liver experts have commented that it is implausible that the clinical condition of these patients would have allowed them to have been safely discharged before they had clinically improved to a sufficient degree.

An analysis of average length of inpatient stay data is presented in this submission to refute the theory that the findings of the 'real world' audits were not driven by strategies to decrease bed stay employed by the NHS in England & Wales. Feedback from expert hepatologists conducting the audits also confirms that the reductions seen in both length of stay and admissions is not merely a result of any such strategies, but reflect a consistent and reproducible treatment effect.

4. a) Long term effectiveness

A central aspect of the unpublished FAD commentary that led to a negative decision related to the Committee's interpretation of clinical opinion and specific real world data submitted by the clinical expert Dr. Debbie Shawcross. The argument laid out by the Committee Chair essentially contended that rifaximin-α had peak effect at three months and then there was a subsequent waning of effect. The Company has specifically addressed this by:

- reminding the Committee of the 24 month open-label study data (Mullen et al 2014 [1]) and
- presenting a meta-analysis of four published independent NHS audits and to aid the Committee's understanding of the long term benefits of rifaximin-α.

b) Effect on mortality

The Committee considered there were uncertainties in the economic model due to the assumptions made around mortality benefit. To support the mortality assumptions based on the RFHE 3002 data additional publications are cited. These

data support the plausibility of the modelled mortality benefit and indicate that the magnitude is not unreasonable

Rationale for Applying Minimal Important Difference for Utility Assumptions in the Economic Modelling

1. Introduction

This section of the fourth submission to NICE reviews the literature for quality of life (QoL) for patients with liver cirrhosis with particular attention to decompensated patients and those with hepatic encephalopathy. In addition, a review of 'minimal important difference' is included to provide further important evidence to reduce the uncertainty in the utility values used in the economic modelling for rifaximin-α and to determine the most likely minimal value for utility seen for patients with hepatic encephalopathy treated with rifaximin-α.

2. Background

To date Norgine has made three submissions to NICE. In the original submission, considered at the first Appraisal Committee meeting in May 2013, utilities from a preference-based exercise involving members of the UK general public were used [2]

At the first Committee meeting Norgine were directed to utilise data from the pivotal randomised placebo controlled study, RFHE3001, [3, 4] to calculate utilities [5]. The approach used in Norgine's second submission to NICE was to utilise published QoL data using the Chronic Liver Disease Questionnaire (CLDQ) from RFHE3001 study [6] and map those values to EQ-5D scores derived from the SF-36 results from the same study. This indirect approach was used due to the following data related factors:

- Concern having been expressed about the reliability of QoL assessment in cognitively impaired patients using generic instruments [7]
- The higher relative proportion of missing data with the optional SF-36 questionnaire (35/299 or 11.7%) compared to the mandatory CLDQ questionnaire (5/218 or 2.3%) (despite the CLDQ dataset being limited to patients in Canada and the USA because a validated Russian translation was not available)
- Evidence that that cognitively impaired patients can reliably and consistently respond to disease-specific questionnaires [8] .
- Use of a greater number of study measurements from both scores in the chosen indirect approach (where the analysis makes use of both SF-36 and CLDQ data sets in the derivation of the utilities as opposed to the direct approach which relies solely on the SF-36 dataset)

A more recent review [9] of the assessment of QoL in subjects with cognitive impairment resulting from acquired or degenerative brain injury confirmed that:

> *"… only a few measures have been developed and validated for respondents with cognitive impairment, often showing poorer validity results than studies*

involving healthy persons. Health-related quality of life assessment should therefore be validated in the specific diseases and, if necessary, combined with a neuropsychological evaluation and a disease-specific health-related quality of life measure."

At the second Appraisal Committee meeting in October 2013 concern was expressed about the indirect approach used by Norgine and the Committee directed Norgine to submit a model using utilities derived directly from the SF-36 [10]. The work was undertaken and submitted to NICE and was considered at the third Committee meeting in April 2014. The Committee considered the revised model but doubts were expressed about the magnitude of utility gain in patients treated with rifaximin-α.

3. Published utility scores in patients with HE

It is not unexpected, given the limited QoL data on patients with chronic liver disease that few publications report utility scores for patients with CHE or OHE.

Data specific to patients with HE were published in 2004 by Wells et al [11] where utilities of 0.55 ±0.22 were reported for patients with HE whereas patients with decompensated cirrhosis without HE had scores of 0.74 ±0.2.

Utility values have been published for patients with compensated and decompensated disease using a variety of methodologies [12-15]. In a systematic review McLernon et al from 2008 [16] reported a meta-regression model that was fitted to the data with a pooled estimate for EQ-5D utility in patients with decompensated disease of 0.672

Recent Health Technology Appraisals undertaken by NICE for hepatitis treatment (for example the ongoing sofosbuvir for chronic hepatitis C ID654 [project documents available at http://www.nice.org.uk/guidance/indevelopment/gid-tag445/documents - accessed October 6 2014]) have used utility values published in 2006 by Wright et al [17] with values for compensated and decompensated cirrhosis of 0.55 and 0.45 respectively.

In the absence of published data on utility values for specific health states in patients with HE Norgine commissioned a study that involved members of the UK public [2]. The results are summarised below.

Table 1: Mean utilities (95% confidence intervals) for five health states in patients with hepatic encephalopathy elicited from the UK general public [2]

	Conn Score				
	0	1	2	3	4
TTO	0.962	0.912	0.828	0.691	0.429
CI	0.952; 0.972	0.896; 0.929	0.803; 0.852	0.656; 0.726	0.371; 0.487
SG	0.915	0.837	0.683	0.489	0.215
CI	0.897; 0.932	0.816; 0.858	0.657; 0.709	0.459; 0.519	0.190; 0.240

TTO – Time Trade Off; SG – Standard Gamble; CI – Confidence Interval

These values, particularly for Time Trade Off would seem to be higher than previously published values for patients with decompensated cirrhosis (see above).

4. Quality of Life effects of rifaximin-α in patients with hepatic encephalopathy from the RFHE3001 study (Bass et al [3])

In the pivotal clinical trial, RFHE3001, patients completed the disease specific Chronic Liver Disease Questionnaire (CLDQ) and the generic SF-36. Patients were recruited in the USA, Canada and Russia. Whilst the SF-36 has been validated in each of those countries, the CLDQ was only available for the USA and Canada.

SF-36 was specified as an optional instrument by the RFHE3001 study protocol whereas CLDQ was a mandatory assessment at each study visit. The protocol amendment journal (vol 5, CSR) shows that although SF-36 was originally specified as a mandatory assessment, its status was changed to optional after only 2 months, due to difficulties reported by investigators and their patients in completing the instrument. It is interesting to note that another study also reported a significant proportion of patients with HE failed to complete the SF-36 questionnaire [18]. This is reflected in the higher proportion of missing data for SF-36 than CLDQ observed in the RFHE3001 data (the proportion of patients not completing either questionnaire was 11.7% for SF-36 (35/299) vs 2.3% for CLDQ (5/218) [the denominator difference is due to absence of a Russian translation for CLDQ]). This serves to weaken the case for SF-36 as a direct measure of between-treatment-group difference in patient-reported quality of life.

This does not however preclude the use of the SF-36 data to either estimate EQ-5D index utility for each observation or to enumerate the relationship between CLDQ and utility where simultaneous observations were available.

Given that Norgine has incorporated the measurable uncertainty of both the incremental treatment time-weighted difference in CLDQ Overall score [6] and the parameter estimate of the CLDQ-EQ5D mapping function, we believe this approach to be more satisfactory than a direct between-treatment-group assessment of EQ-5D utility which would be confounded by the optional status of the SF-36 instrument and the un-quantifiable bias introduced by the higher prevalence of missing data.

It is worth stating that, of the 2 methods for deriving utility (using only SF36 data directly vs using both CLDQ and SF36 data from the study in the manner chosen by Norgine); the method used by Norgine makes use of the higher quality dataset and indeed uses more of the study data (a greater number of observations) to generate what is arguably a truer reflection of the real changes in HrQol observed in these patients. It is Important to remember, as highlighted above, that concern has been expressed about the reliability of generic QoL instruments in cognitively impaired patients [7, 9] but that they may reliably and consistently respond to disease-specific questionnaires [8]

Table 2: Comparison of the two methods used to calculate utility

Method of deriving utility	Direct derivation from SF36	Derivation via mapping to CLDQ
HrQol data set used	**SF36 only**	**SF36 and CLDQ**
Quality of data sets used	**Poorer** (optional assessment using ***less-sensitive generic*** instrument (SF36) to detect change in QoL which is incompletely recorded)	**Higher** (use of a mandated assessment of more ***sensitive disease specific*** instrument (CLDQ) to detect change in QoL – more completely recorded)

The QoL results from the pivotal clinical trial were published as a post-hoc analysis [6] that calculated time-weighted average CLDQ scores rather than the pre-specified change from baseline analysis [4]. In the per-protocol analysis there was no difference between the two treatment groups at the end of the study for either the SF-36 or CLDQ [4]. In the post-hoc time-weighted analysis however overall CLDQ score and each domain score were significantly higher in the rifaximin-α group vs. placebo (P-values ranged from 0.0087 to 0.0436) [6].

In another study that enrolled patients with covert HE with no previous episodes of overt HE significant differences between rifaximin-α treated patients and placebo were reported in the total Sickness Impact Profile (SIP) score at the end of the 8 weeks of the study [19]. In addition there were significant differences in six SIP scales and the total psychosocial and physical sub-scores. It is important to note that patients enrolled in the RFHE3001 study were also in the covert HE state, as identified by baseline Conn scores of 0 or 1, but had at least 2 prior episodes of HE. In this study the magnitude of improvement was much greater than the 10% that reported in the pivotal clinical trial [3, 6].

In a second 8-week study that also evaluated patients with covert HE significant improvements in the psychosocial scale of the SIP following treatment with rifaximin-α were reported [20] as well as improvements in cognitive function and driving simulator performance.

5. Utility values derived from rifaximin-α clinical trial RFHE3001

At the first Appraisal Committee Norgine was directed to use data within the RFHE3001 clinical trial to estimate utility values rather than the UK population derived values used in the first submission[5]. In the RFHE3001 study patients completed the disease specific Chronic Liver Disease Questionnaire (CLDQ) and the generic SF-36; the SF-36 was optional.

As previously stated the proportion of patients not completing the SF-36 questionnaire was 11.7% (35/299) and 2.3% (5/218) for CLDQ. (The denominator difference is due to the absence of a validated Russian translation of CLDQ.)

In a post-hoc analysis of the trial data, Sanyal et al [6] demonstrated that time-weighted averages of the overall CLDQ score and each domain score were significantly higher in patients treated with rifaximin-α than those who received placebo. These data were used to derive utilities for the second submission to NICE.

The CLDQ results were mapped into utility using a two-step approach. First SF-36 data from the trial was converted into utilities using the response-mapping algorithm developed by Gray et al [21]. Next, General Estimating Equations (GEE) modelling was used to quantify the relationship between overall CLDQ score and estimated utility. CLDQ Overall score as a significant predictor ($p<0.001$) of estimated utility with each additional unit CLDQ score confers an incremental utility of 0.143 (95% CI 0.131 to 0.154).

The baseline covert state utility value was 0.588; applying the mean improvement reported by Sanyal et al [6] for rifaximin-α treated patients gave a utility value of 0.694. Hence, patients treated with rifaximin-α experience a higher utility while in the covert state than patients treated with standard of care, the difference being 0.106 These values are consistent with published data for patients with compensated and decompensated disease (see above). The difference between patients in the overt HE state and the covert HE state (0.106) may be compared to the difference between decompensated and compensated patients reported by Wells et al [11] of 0.19 and Wright et al [17] of 0.10. The Wright et al values have been used in NICE appraisals for viral hepatitis treatments (see above)

At the second Appraisal Committee meeting, concern was expressed about the two-step modelling approach to calculate utilities and the Committee concluded that mapping directly from the SF-36 data to EQ-5D would be more appropriate [10]. Using this methodology a utility benefit in the covert state for rifaximin-α treated patients compared with standard of care of 0.032 was calculated.

Possible reasons for the substantial differences between the two estimates include:

- Greater proportion of missing data for the SF-36 than the CLDQ in the RFHE3001 study that could have introduced non-random bias
- Problems with generic instruments in patients with cognitive impairment [7, 9] that may not apply to disease specific questionnaires [8] (see above).
- More observations used in Norgine's preferred method using both SF-36 and CLDQ data (compared to the direct approach which used the SF-36 dataset only and disregarded the disease specific CLDQ dataset.

In view of the differences between the two estimates of utility gain in patients treated with rifaximin-α compared with standard of care, consideration was given to sources that might provide information as to the clinical plausibility of the alternative values.

6. Quality of Life improvements in UK Clinical Practice

In parallel to the various NICE appraisal processes, Norgine has had ongoing discussions with clinical experts to gather insights into the condition of hepatic encephalopathy and how it is treated in current UK clinical practice.
These experts include:

- Dr Debbie L Shawcross, Senior Lecturer and Honorary Consultant in Hepatology, King's College Hospital,London

- Dr Mark Hudson, Consultant Hepatologist, Freeman Hospital, Newcastle
- Dr Dillon, Clinical Reader in Hepatology and Gastroenterology, Ninewells Hospital, Dundee, Scotland
- Dr Aspinall, Consultant Hepatologist, Queen Alexandria Hospital, Portsmouth
- Dr Goel, Senior Specialist Registrar, Royal Preston Hospital, Preston
- Dr Richardson, Consultant Hepatologist, The Royal **Liverpool** and Broadgreen University Hospitals, Liverpool
- Prof Hayes, professor of Hepatology, Edinburgh Royal Infirmary, Edinburgh
- Dr. Jim Orr, Clinical Research Associate and Clinical Registrar, Royal Victoria Hospital, Newcastle

In particular, Norgine has sought expert opinion as to whether there is an observable clinical benefit seen in patients with HE when treated with rifaximin-α. Feedback from clinical experts confirms that observable clinical improvements are indeed seen in patients treated with rifaximin-α in both overt HE and covert HE.

There were some general comments around the difficulties associated with the gathering of QoL data in HE patients:

- In the trials, it would have been difficult to obtain QoL values for patients with high Conn scores, because these patients would not have the cognitive ability to respond.
- The family/carer is better placed to notice more changes in QoL day to day than the physician
- QoL usually does not go back to 'baseline' after an overt HE episode.

A published case study highlights the substantial QoL improvements that treatment with rifaximin-α can bring. Reddy et al 2012 reported significant improvements in handwriting and artistic ability were seen in a patient with HE following treatment with rifaximin-α. This improvement in overall function enabled the patient to complete their postgraduate study and gain a Masters qualification. This case study demonstrates that treatment with rifaximin-α for HE can bring about significant change in functioning for an individual patient.

When asked if they were able to quantify the clinical benefit seen with rifaximin-α in terms of a percentage improvement, clinical experts found this impossible. However, one of the clinical experts made the following comment, with which the other experts concurred:

> "It is unanimous among physicians that [rifaximin-α] works and that there are clinically significant improvements in QoL…if the [utility] benefit was actually just 0.03 it is unlikely that there would be such unanimity".

Several experts felt that comments from in the ACD regarding a decreasing clinical efficacy over time were fundamentally wrong.

Further quotes from clinicians with significant experience of rifaximin-α:

> "This drug has been life changing for my patients"

From the author of one of the audits when asked if there was a clinically observable difference in the QoL of patients treated with rifaximin-α:

> "We didn't measure this in the audit. From a clinical perspective we do see an observable difference in patients who are prescribed [rifaximin-α] in our clinics"

Another commented:

> "The data for the efficacy of [rifaximin-α] in HE cannot be disputed given the RCT trials. Everyone that uses [rifaximin-α] has seen a massive difference and improvement in their patients in a clinical setting"

7. Minimum Important Difference in Utility Values

As described above (Section 6, Quality of life Improvements in UK Clinical Practice), clinicians and patients unanimously report a ***clearly*** observable improvement in QoL following initiation of rifaximin-α treatment in the context of background pre-existing lactulose treatment. This suggests that rifaximin-α achieves at the very least a clinically minimally important difference (MID).

There has been widespread determination of MID across a range of disease states. In Walters and Brazier [22] the overall MID across 8 different conditions was 0.074. In their recent review Coretti et al [23] reported EQ-5D MID values from 17 additional publications with values ranging from 0.03 to 0.52 with 14 reporting at least one value >0.10 (see Table 3).

Table 3: Minimal important differences in utility scores across acute and chronic conditions (adapted from Walters and Brazier, 2005 [22] and Coretti et al 2014 [23]

Disease	Original Author	EQ-5D MID
Walters & Brazier		
Leg ulcer	Walters et al 1999	0.139, 0.109
Back pain	Thomas et al 2003	0.081
Early rheumatoid arthritis	Allard et al 2000	0.129
Limb reconstruction	Burton et al 2003	0.054
Irritable bowel syndrome	Akehurst et al 2002	0.065, 0.035
Acute myocardial infarction	Lacy and Walters 2003	0.089
Knee osteoarthritis	Brazier et al 1999	0.121
Chronic obstructive pulmonary disease	Harper et al 1997	-0.011, 0.00
	Overall	*0.074*
Coretti et al		
Hip arthroplasty	Larsen et al 2008	0.08
Rheumatoid arthritis	Marra et al 2005	0.05
Lumbar disc herniation surgery	Solberg et al 2013	0.3
Low back pain	Soer et al 2012	0.03
Surgery for cervical radiculopathy	Parker et al 2012	0.24
Revision fusion for pseudoarthrosis back pain	Parker et al 2012	0.14 – 0.24
Surgery for femoroacetabular impingement	Impelizzeri et al 2012	0.16
Revision surgery for recurrent stenosis associated back and leg pain	Parker et al 2012	0.29 – 0.52
Transforaminal lumbar interbody fusion	Parker et al 2011	0.15 – 0.54
Intervertebral disc herniation	McDonough et al 2011	0.12, 0.25, 0.15, 0.14
Ankylosing spondylitis	Boonen et al 2007	0.36
Surgery for inguinal hernia	Staerkle et al 2011	0.36
Multiple myeloma	Kvam et al 2011	0.08 – 0.10
Advanced cancer	Pickard et al 2007	0.10 – 0.12
Post traumatic stress disorder	Le et al 2013	0.05 – 0.08, 0.04 – 0.10
Inflammatory bowel disease	Stark et al 2010	0.076
Moderate to severe plaque psoriasis	Shikiar et al 2006	010, 0.20, 0.09

8. Conclusion

Experienced clinicians who use rifaximin-α consistently report a **clinically observable** difference in QoL vs standard of care (i.e. lactulose alone). This logically

implies that the magnitude of this difference must, at the very least, be above the "detectability" level of the clinically minimally important difference (MID).

Published values for the MID for the EQ-5D for a utility improvement to be detectable range from -0.011 to 0.54. Only one report has a value of <0.03 but the authors concluded that *'The results from this study suggest that the EQ-5D is inappropriate for use in this patient group'* (COPD) [24].

Therefore, in order to be observable the improvement in health-related utility would need to be at least 0.03 units. It should, however, be clearly stated that this value is the ***most conservative*** one for the EQ-5D MID, and represents the lower limit of the range of plausible values for the EQ-5D MID found in the literature.

Norgine believes however that existing evidence does provide sufficient insight to allow for a base-case assumption that there is a difference of 0.106 units in utility in the covert state which is both plausible and defensible, particularly in light of the recent review by Corretti et al [23] on MID values across a range of conditions and the difference in utility values between patients in the compensated and decompensated states from two studies of 0.19 [11] and 0.10 [17].

9. Effect of utility assumptions on economic model results

As well as the Norgine base-case (utility value 0.106) sensitivity analyses using the SF-36 (only) derived base-case (utility value 0.032) and the utility value (0.074) supported by the MID data published by Walters & Brazier [22] are presented here.

Table 4: ICER values derived using different utility assumptions

Covert Utility Assumption	Covert Utility Benefit	5 Year ICER	10 Year ICER	Lifetime ICER
Norgine Basecase	0.106	£20,702	£19,241	£17,810
Walters and Brazier	0.074	£25,907	£23,549	£21,331
Direct SF 36/EQ 5D Derived (TAC requested)	0.032	£38,669	£33,349	£28,805

The Norgine basecase shows rifaximin-α to be cost effective (ICER <£30,000) when 5 year, 10 year and lifetime horizons are applied.

Using the 0.032 utility (derived solely from SF-36 data) rifaximin-α is seen to be cost effective (ICER <£30,000) when a lifetime horizon is applied.

However the MID data supports a utility value somewhere between 0.032 and the Norgine base case of 0.106. Using the Walters & Brazier MID derived value of 0.074 rifaximin-α is shown to have ICERs <£30,000 for 5 year, 10 year and lifetime treatment horizons.

Norgine contends that, by using this MID data, uncertainties surrounding the utility value are reduced and that utility values below 0.032 should not be included in any sensitivity analyses. Furthermore the MID data suggests that ICERs for rifaximin-α are closer to the Norgine base case than to those derived solely from SF-36 data.

This would suggest that the most plausible scenario is that rifaximin-α is cost effective.

Section 2. Application of Real World Data to the Economic Case for TARGAXAN 550mg (rifaximin-α).

Whilst many appraisals of new products rely solely on economic modelling to predict cost effectiveness this is not the case for rifaximin-α which has been adopted as a treatment option for patients with hepatic encephalopathy in evidence based clinical practice in many UK centres. A number of centres have had the opportunity to examine the impact of rifaximin-α in a 'real world' context and have published the results of their audits. (See Appendix C)

To enable useful comparisons of annualised rates of hospitalisation and hospital length of stay only the data from Dundee, Bristol, Newcastle and Bolton are used [25-28]. The analysis was limited to data from these four centres as these were the first independently published real world audits of the use of rifaximin-α in the management of HE in the UK, and which a minimum duration of exposure to drug of at least 6 months.

The King's combined multicentre data [29], though qualitatively informative, are too heterogeneous and of too short a duration (i.e. less than 6 months) to be included in this analysis. Recently, another centre (Portsmouth) [30] has independently published their experience of use of rifaximin-α reporting reductions in hospitalisations consistent with the above publications. This data from Portsmouth was however published too recently to be included in the analysis. It is referenced here for transparency, enabling sensitivity analyses including / excluding these new data.

Each study analysed data from people treated with rifaximin-α before and after their exposure to the drug. A preliminary descriptive analysis of these studies presented to NICE in July 2014 suggested that rifaximin-α had a consistent impact on not only risk of hospital admission (combined reduction of 46%), but also length of hospital admissions (combined reduction 45%) resulting in an estimated 70% reduction in bed utilisation (range 59% to 90%) across the four hospital audits.

Table 5. Preliminary combined analysis of audit data from four UK hospitals evaluating the impact of rifaximin-α treatment on hospital utilisation.

		Annualised hospitalisations rate				Mean HLOS			
	n studied	Before	After	Δ	Δ (%)	Before	After	Δ	Δ (%)
Dundee	16	1.8	0.9	0.9	47.8	7.6	4.9	2.7	35.5
Bristol	16	2.3	1.3	1.0	43.5	14.6	10.6	4.0	27.4
Newcastle	64	2.7	1.8	0.9	33.3	10.5	5.2	5.3	50.4
Bolton	24	4.0	1.0	3.0	75.0	6.9	2.5	4.4	63.6
Totasl/weighted mean	120	2.8	1.5	1.3	46.4	9.9	5.4	4.5	45.5

		Annualised total bed days				Monthly total bed days			
	n studied	Before	After	Δ	Δ (%)	Before	After	Δ	Δ (%)
Dundee	16	13.8	4.6	9.1	66.4	1.1	0.4	0.8	66.4
Bristol	16	33.6	13.8	19.8	59.0	2.8	1.1	1.7	59.0
Newcastle	64	28.4	9.4	19.0	66.9	2.4	0.8	1.6	66.9
Bolton	24	27.5	2.5	25.0	90.9	2.3	0.2	2.1	90.9
Totasl/weighted mean	120	27.7	8.1	19.6	70.8	2.3	0.7	1.6	70.8

The following analysis addresses uncertainty in the combined effect suggested by these published real-world findings.

METHODS

Data

The published results from each study were transformed into annualised endpoints with mean and standard deviation (SD). From the Bolton study [25], median and range were converted to mean and SD using the method described by Hozo et al for small samples [31]. For the Bristol and Dundee studies [27, 28], SD was estimated by conservatively assuming p=0.05 (Roach reported p<0.05 for both endpoints), a common SD, and a two-sided unpaired Student's t-test [32].

Endpoints

Two endpoints are analysed, hospitalisations and total bed days. A constant event rate was assumed in annualising the data presented by each study, which had varying observation periods.

Statistics

Meta-analysis was conducted using OpenMeta[Analyst] software [33-35]. Mean difference in each primary endpoint was tested with a continuous random-effects model using the DerSimonian-Laird method to allow for heterogeneity between studies.

RESULTS

The input data for each endpoint is given in table 6 and table 7

Table 6. Annualised per patient hospitalisation rate input data

Author	Centre	Year of study	Observation time	BEFORE RIFAXIMIN			AFTER RIFAXIMIN		
				N	*Mean*	*SD*	*N*	*Mean*	*SD*
Roach et al.	Dundee	2013	variable	16	2.1	1.6	16	0.9	1.6
Valliani et al.	Bristol	2010	12 months	12	2.3	0.9	4	1.3	0.9
Orr et al.	Newcastle	2011	12 months	27	2.7	2.4	27	1.8	2.9
Goel et al.	Bolton	2013	6 months	24	5.0	2.4	24	3.0	2.3

Table 7. Annualised per patient bed days input data

Author	Centre	Year of study	Observation time	BEFORE RIFAXIMIN			AFTER RIFAXIMIN		
				N	*Mean*	*SD*	*N*	*Mean*	*SD*
Roach et al.	Dundee	2013	variable	16	16.2	17.59	16	3.5	17.59
Valliani et al.	Bristol	2010	12 months	12	34.0	14.94	4	15.5	14.94
Orr et al.	Newcastle	2011	12 months	27	28.4	26.30	27	9.4	14.70
Goel et al.	Bolton	2013	6 months	24	92.0	72.20	24	30.0	31.79

The pooled estimate for mean difference in annual hospitalisations per patient before and after rifaximin-α treatment is 1.254 (95% CI 0.661 to 1.829; p<0.001). Heterogeneity between studies is observed to be low and non-significant (figure 1). Weighting baseline hospitalisation according sample size and variance (Newcastle, 16.9%; Bolton, 19.5%; Bristol, 34.8%; and Dundee, 28.7%), the pooled estimate equates to a 44% reduction after rifaximin-α treatment.

The pooled estimate for mean difference in annual bed days per patient before and after rifaximin-α treatment is 22.184 (95% CI 9.095 to 35.273; p<0.001). Heterogeneity between studies is observed to be high (63%) and statistically significant (p=0.043: (Figure 2) Weighting baseline hospitalisation according sample size and variance (Newcastle, 32.1%; Bolton, 12.2%; Bristol, 24.8%; and Dundee, 30.9%), the pooled estimate equates to a 66% reduction after rifaximin-α treatment.

Sensitivity analysis excluding the Bolton study reduces heterogeneity (Figure 3), and the pooled estimate for mean difference in annual bed days per patient before and after rifaximin-α treatment is 16.543 (95% CI 9.084 to 24.003; p<0.001), also a 66% reduction after rifaximin-α treatment.

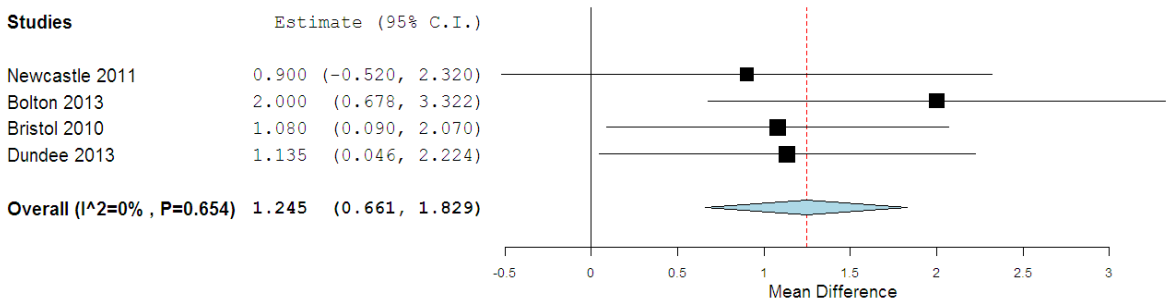

Figure 1. Forest plot of mean difference in annual hospitalisations per patient before and after rifaximin-α treatment

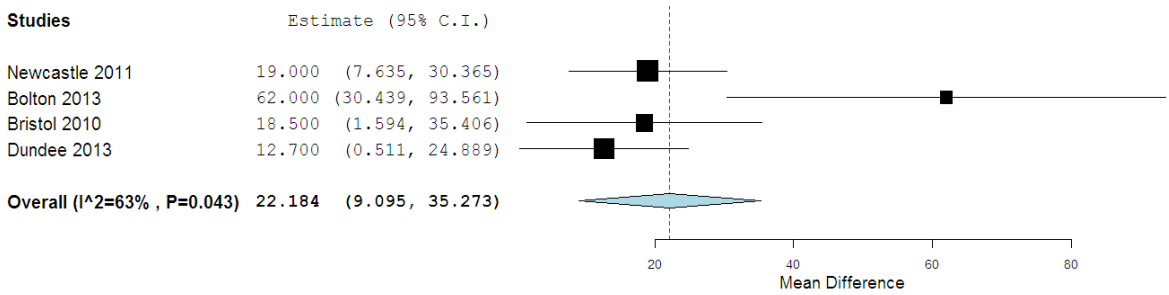

Figure 2. Forest plot of mean difference in annual bed days per patient before and after rifaximin-α treatment

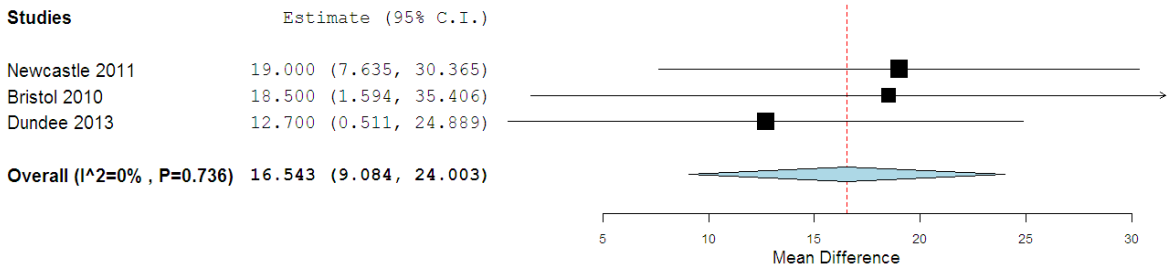

Figure 3. Forest plot of mean difference in annual bed days per patient before and after rifaximin-α treatment (excluding Bolton study).

OTHER 'REAL WORLD' DATA

Analysis of the impact of rifaximin-α on hospitalisation rates, length of stay and the impact on costs have also been reported from two US hospitals in a number of publications [36-40]. Results were very similar to that seen in the UK audit data. Interestingly the results reported by Leevy et al from Newark, New Jersey [37] were very similar to that seen in the pooled analysis from four UK sites described above.

CONCLUSION

Despite small sample sizes and evident heterogeneity between studies, consistent reductions in hospitalisations and admitted bed days are observed for which the pooled estimates are statistically significant. Similar results have been reported from the USA. This suggests a consistent pattern of reductions in these two important outcome measures and provides consistent complementary evidence to the findings of the randomised controlled study (Bass et al 2010 [3]) which reported an approximate halving of hospitalisation rate with rifaximin vs placebo in patients with a history of recurrent HE.

Updated Economic Model Outputs Based on Real World Data Effects on Resource Reduction

The inputs of the cost-utility model have been adjusted in order to simulate the annualised outputs observed in the meta-analysis of UK RWD. The most striking difference between the Norgine base case and the UK RWD is the annual bed days occupied, 2.9 per patient per annum using original base case assumptions, of which the observed number in UK clinical practice is nearly ten times greater (Table 8).

Table 8. Year 1 hospital resource utilisation under Norgine basecase assumptions and those observed in UK RWD.

A) Norgine basecase

		prob hosp	LoS		
LACTULOSE		53%	5.0		
	6 months	374	admissions		
		1,872	bed days		
		0.37	adm per patient		
		1.87	bdays per patient		
	12 months	584	admissions		
		2,922	bed days		
		0.58	adm per patient		
		2.9	bdays per patient	Mean Difference	1.4

		prob hosp	LoS		
RIFAXIMIN		53%	5.0		
	6 months	178	admissions		
		888	bed days		
		0.18	adm per patient	53%	reduction
		0.89	bdays per patient	53%	reduction
	12 months	304	admissions		
		1,522	bed days		
		0.30	adm per patient	47.9%	reduction
		1.5	bdays per patient	47.9%	reduction

B) RWD (4 centres)

		prob hosp	LoS					prob hosp	LoS		
LACTULOSE		100%	30.6			RIFAXIMIN		100%	20.2		
		708	admissions					336	admissions		
	6 months	21,665	bed days				6 months	6,783	bed days		
		0.71	adm per patient					0.34	adm per patient	53%	reduction
		21.66	bdays per patient					6.78	bdays per patient	69%	reduction
		1,105	admissions					576	admissions		
	12 months	33,822	bed days				12 months	11,625	bed days		
		1.11	adm per patient					0.58	adm per patient	47.9%	reduction
		33.8	bdays per patient	Mean Difference	22.2			11.6	bdays per patient	65.6%	reduction

C) RWD (3 centres [Bolton removed])

		prob hosp	LoS					prob hosp	LoS		
LACTULOSE		100%	22.5			RIFAXIMIN		100%	14.6		
		708	admissions					336	admissions		
	6 months	15,930	bed days				6 months	4,912	bed days		
		0.71	adm per patient					0.34	adm per patient	53%	reduction
		15.93	bdays per patient					4.91	bdays per patient	69%	reduction
		1,105	admissions					576	admissions		
	12 months	24,869	bed days				12 months	8,418	bed days		
		1.11	adm per patient					0.58	adm per patient	47.9%	reduction
		24.9	bdays per patient	Mean Difference	16.5			8.4	bdays per patient	66.2%	reduction

The effect of increasing the first year bed days in the standard of care arm is illustrated in Table 9. Using the mean difference in bed days observed in UK RWD, at all time horizons and covert utility scenarios (including zero benefit), rifaximin-α is either dominant over or cost-effective against lactulose. The dominance of rifaximin-α in early years of treatment is particularly evident, driven by the materially higher bed day usage which effectively offsets the acquisition cost of rifaximin-α over current standard of care.

Table 9. Incremental cost-effectiveness ratios (£/QALY) assuming hospital inpatient resource use equivalent to that observed in routine practice

A) RWD base case (4 studies)

Covert utility benefit	RWD effect	ICERs Year 5	Year 10	Lifetime
0.106	*Lower*	£17,064	£17,809	£17,279
	Mean	**Dominant**	**£4,466**	**£7,205**
	Upper	Dominant	Dominant	Dominant
0.074	*Lower*	£21,354	£21,796	£20,695
	Mean	**Dominant**	**£5,465**	**£8,630**
	Upper	Dominant	Dominant	Dominant
0.032	*Lower*	£31,874	£30,867	£27,947
	Mean	**Dominant**	**£7,740**	**£11,654**
	Upper	Dominant	Dominant	Dominant

Baseline bed days 33.8 days per patient per year
Lower – the lower bound limit of the 95% CI for the mean difference in bed days;
Mean – the mean difference in bed days between SoC and rifaximin-α, and;
Upper – the upper bound limit of the 95% CI for the mean difference in bed days.

B) RWD sensitivity analysis (excluding Bolton)

Covert utility benefit	RWD effect	ICERs Year 5	Year 10	Lifetime
0.106	*Lower*	£15,028	£15,954	£15,720
	Mean	**£4,844**	**£8,462**	**£10,063**
	Upper	Dominant	£758	£4,247
0.074	*Lower*	£18,806	£19,526	£18,828
	Mean	**£6,062**	**£10,357**	**£12,053**
	Upper	Dominant	£928	£5,087
0.032	*Lower*	£28,070	£27,651	£25,425
	Mean	**£9,049**	**£14,667**	**£16,276**
	Upper	Dominant	£1,314	£6,869

Baseline bed days 24.9 days per patient per year;
Lower – the lower bound limit of the 95% CI for the mean difference in bed days;
Mean – the mean difference in bed days between SoC and rifaximin-α
Upper – the upper bound limit of the 95% CI for the mean difference in bed days

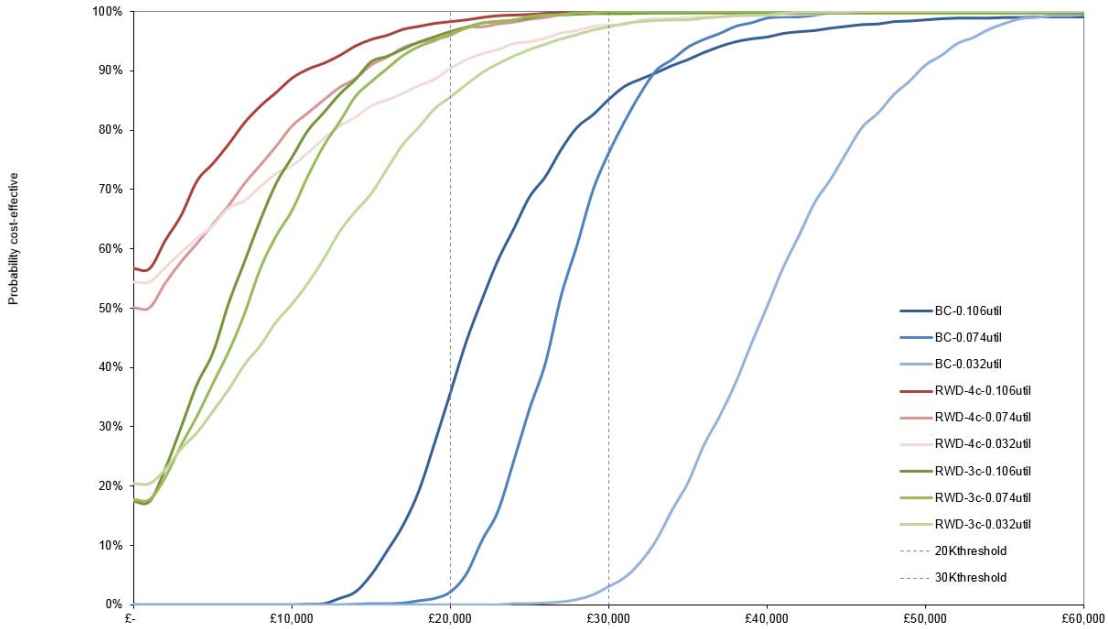

Figure 4. CEAC for base case (BC) and real-world data (RWD) scenarios with alternative covert utility benefit for rifaximin-α

<u>Discussion of the real world audit data</u>

Introduction

The efficacy of rifaximin-α in reducing episodes of recurrent hepatic encephalopathy has been demonstrated through RCT evidence in the RFHE3001 pivotal clinical trial [3, 6] and the 24 month open-label extensions study RFHE3002 [1].

In the RFHE3001 study, rifaximin-α brought about significant reductions in hospitalisations from overt HE episodes over the six month duration of the study vs placebo (>90% of patients in both arms were receiving concomitant lactulose). As with any randomised controlled clinical trial the external validity of the study and hence generalizability has limitations due to, for example, the necessarily of having strict inclusion/exclusion criteria and in particular as it was not conducted in the UK. However, the results of this high quality study have had a significant impact on UK clinical practice.

Unlike most new treatments, rifaximin-α has been available in Europe for many years and, in some UK centres, has been adopted as a treatment option in the management of patients with hepatic encephalopathy.

Several centres have carried out independent audits on cohorts of patients who were treated with rifaximin-α to explore the impact on hospitalisations and length of stay of these patients and, by consequence, the cost-effectiveness of its use at a local level. These audits have employed similar methodologies whereby patients were identified retrospectively through pharmacy records and hospital records were reviewed to investigate any differences in hospital admissions or length of stay in the periods before and after rifaximin-α treatment, whereby the patient acts as their own 'control'.

As seen in the meta-analysis the results demonstrate consistent reductions in length of stay and hospital admissions across individual centres. Whilst the numbers from each individual centre are small, the fact that these trends are replicated across geographically disparate centres at different times adds weight to the conclusion that the effect on hospitalisations in terms of frequency and duration, appears to be real and that rifaximin-α treatment is cost saving to the NHS in the real world setting.

Real world Data - Strengths and Limitations

There has been well documented criticism of randomised controlled clinical trials and their relatively selected populations and the applicability of results to a real world setting where patients and their treatments are much more heterogeneous and certain safety signals emerge only over periods of time longer than the average clinical trial. Thus the concept of observing outcomes in a real world setting and using these observations to make inferences about a treatment's safety, effectiveness and cost effectiveness when used in the relatively less controlled setting of the 'real world' has emerged.

The accepted concept of a hierarchy of evidence has also been challenged and it has been argued that a more appropriate means of determining a new treatment's effectiveness is to accept a diversity of approaches to the available evidence. This involves embracing both RCT data ***and*** observational real world data and applying expert judgement to all the evidence in the context of its use (Rawlins 2008 [41] This seems pertinent to the current situation with rifaximin-α where the RCT data whilst, Grade 1+ in hierarchy, has good, but limited applicability to a real world UK setting. It is for this reason that consideration of real world evidence from UK clinical practice warrants further consideration.

Hepatic Encephalopathy (HE)

There is widespread acknowledgement that HE is a poorly understood condition and there is limited consensus about all aspects of its management. Excluding those cases where the liver is normal and HE develops due to porto-systemic shunting, HE is a condition that is a manifestation of an underlying liver disease, rather than a disease in itself, and may be difficult to identify but has potentially significant impact on patients, carers, families and health and systems. Indeed recent evidence shows that cirrhotic patients with HE are at greater risk of death than matched cirrhotic without HE (Report submitted to NICE 2nd Committee Meeting 2013 [42])

It is a condition that is subject to variability in coding within health systems hence there is considerable uncertainty around the cost impact of the condition in UK clinical practice. As baseline data is scarce and poorly coded, specific comparative data when new treatments emerge are difficult to identify. A reasonable measure to explore treatment effectiveness in this condition is available in the form of hospital admission and length of stay data as patients with this condition who experience overt episodes are unwell and need to be managed in hospital. However, it is important to understand that, since there may be other precipitating causes for an overt HE episode, the occurrence of a single HE episode should not be seen as an indication of treatment failure but the effectiveness of therapy should be viewed over a longer period of time and admissions rates annualised to reflect the nature of the condition.

Several UK centres therefore undertook to gather data around rifaximin-α use in HE by carrying out independent audits on its use. The methodology for all was similar and took the form of a retrospective review of all rifaximin-α treated patients pre and post rifaximin-α. The investigators compared hospital admissions and length of stay before and after rifaximin-α treatment in their centres. The results show a trend towards a reduction in both length of stay and number of hospital admissions for patients receiving rifaximin-α for HE.

Use of rifaximin-α in these audits

In the majority of patients, rifaximin-α has been initiated in the hospital setting to reduce recurrence of overt episodes where there has been at least one prior episode. Rifaximin-α has not been used in primary care or in the outpatient setting in patients who have not had a previous episode of HE. In addition, it may have been used in a patient with covert HE who has had previous overt episodes which are expected to recur in the future (due to underlying progressive liver disease). These patients may be in a covert HE state but remain at risk of further overt episodes.

Baseline assumptions (verified with the authors)

1. Patients in the audits received rifaximin-α according to its licence, for the reduction of recurrence of HE episodes in adults aged >18.

2. The majority (estimated over 60- 75%) of patients received rifaximin-α with concomitant lactulose at therapeutic doses but the proportion of patients receiving lactulose varied according to local clinical practice.

3. As there was no formal specific monitoring in place at any of the centres, compliance of lactulose and rifaximin-α was assumed to be equal across all centres. Rifaximin-α was only available through hospital pharmacies at the time of the audits.

4. It is assumed all non- HE associated drug costs were similar for each patient pre and post treatment at each centre and the only material change was the inclusion of rifaximin-α to the treatment regime. Each patient effectively acted as his/her own control with respect to non- rifaximin-α treatment.

5. Some cohorts included patients who received either 400mg tds or 550mg bd as the dose of rifaximin-α due to the availability of rifaximin-α at the time. It is assumed there is no meaningful difference when either dose is used (i.e. no difference between a total daily dose of 1100mg and 1200mg of rifaximin-α). It is also assumed there is no significant difference between different presentations of similar dose.

6. Variations in care of HE patients may exist between centres but those admitted to hospital have high morbidity and would be unlikely to be discharged unless they had made an observable clinical improvement during the course of their hospital admission. It is therefore assumed that patients were discharged when clinically fit. Any changes to hospital policy promoting earlier discharges either took place before commencement of these audits or could not be applied to patients in the audit due to their clinical condition.

7. The geographical spread represents a reasonable picture of UK wide clinical practice and variations in baseline admissions data may reflect differences in local clinical management or local epidemiological factors.

Limitations of the data

1. To allow for meaningful comparison the analysis presented does not include drug costs spent on patients who died, did not respond or who were incorrectly diagnosed and is limited to patients that had available hospitalisation records pre- & post-rifaximin-α initiation

2. The data do not allow for any comparison of mortality in the rifaximin-α treated population compared to an appropriately matched control group.

3. The analyses were all retrospective in nature.

3. As with any real world observational (non-interventional) data, there is no control for baseline characteristics or severity of disease. No formal clinical protocols are publicly available to identify specific inclusion criteria therefore the patient included have an inherent degree of heterogeneity reflecting UK clinical practice at the time.

4. Limited to no data on deaths or patients lost to follow up are available for individual patients therefore it is not possible to exclude a bias towards responders. In addition, there is no detail in the data on readmissions within 30 days which if extrapolated to the present, has additional resource implications.

5. It is not possible to differentiate between patients receiving rifaximin-α in a palliative context (to improve the quality of the patient' care but with no expectation of prolonging life), those receiving rifaximin-α as long term preventative therapy and/or patients being optimised for transplantation (i.e. 'bridging' treatment) and indeed there may be a degree of overlap. In addition, no differential benefit in these sub-populations can be inferred from the data.

6. Unaccounted costs include treatment costs for patients who died, were transplanted, stopped treatment or moved away and were lost to follow up. Similarly,

any potential benefit in these patients could not be quantified by this methodology as no pre- vs post- comparisons would be possible.

7. The average LOS, annualised hospital admissions, average cost of HE admission (currently being analysed) in the NHS are not known but Norgine understand further work is underway to clarify this.

8. It is not possible to explore the impact of rifaximin-α treatment on the numbers of transplants carried where presence of overt HE was a main contributing indication for transplantation from the data.

Summary

The data carry the expected limitations of a retrospective ”pre & post” approach however there seems to be a consistent trend towards cost savings being evident across the UK. The patients in the audits were not selected for their potential to reduce costs i.e. only those with high number of admissions in previous year, yet the data show consistent reductions in resource utilisation, reflecting similar real world data from the US and consistent with the findings of the randomised controlled pivotal study RFHE3001.

3. An analysis of the effects of NHS policy in England & Wales on reducing hospital bed stay

(see Appendix A Hospital Episode Statistics, 2010-11, 2011-12, 2012-13)

Data from hospital episode statistics (HES) taken for the period of 2011 to 2013 (the period associated with the hospital audit data) has not shown any meaningful reductions in overall hospital bed stay in the hepatology speciality. This is supported by feedback from hepatology centres in England and Wales who have confirmed that the introduction of daily ward rounds designed to reduce bed stay in their hospitals was introduced in 2009/10 which is before the periods of audit.

Guidance from NHS England focused on targeting areas where length of stay was considered too long. Feedback from hepatology specialist centres indicated that they were not considered as target areas for hospital bed stay reduction.

4. Long term effect and effect on mortality of rifaximin-α

4.a Further data to support the long term effect of rifaximin-α.

The long-term effect of rifaximin-α has been shown in the RFHE 3002 open label study (Mullen et al 2014) [1]. This demonstrated a sustained effect over time, which has been supported by real world data audits previously presented to the Committee. Two of these audits, Bristol and Newcastle, followed patients for longer than 6 months. A recent publication from Portsmouth confirmed the continued efficacy of rifaximin-α beyond 6 months.

The results of these studies showed a consistent reduction in hospitalisations for longer than 6 months for these patients.

Long-term efficacy of rifaximin-α is also supported by publications from other countries where follow-up has been up to 5 years (Vlachogiannakos et al 2013 [43],

Neff et al 2012 [44]. Follow-up periods of greater than 6 months have also been reported from a number of international centres Confer et al [45]; Hanouneh et al [46]; Irimia et al [47]

4.b Effect on mortality of treatment with rifaximin-α

In the previous submissions data from RFHE3002 was used to model mortality. (The methods and data synthesis are described in "Addendum to Norgine NICE STA Submission on Rifaximin-α 550mg: Further Analyses in Response to Technology Appraisal Committee's Critique of the Economic Case" submitted to NICE October 2013**.** A review of mortality in HE was submitted as an Appendix at that time.)

The AC accepted a reduction in mortality in patients with HE treated with rifaximin-α was plausible but found the magnitude uncertain. Mortality in both overt and covert states was the same in both cohorts, however, as rifaximin-α treated patients experienced fewer overt episodes mortality was less than in the SOC cohort.

The reduction in mortality seen in the model is supported by a number of publications. In an RCT in patients with overt HE that compared rifaximin-α plus lactulose versus placebo plus lactulose, rifaximin-α treated patients had significantly lower mortality (23.8 % vs. 49.1 %, $P < 0.05$) [48]. It is important to note that this differential effect on mortality has not been included in the model where mortality in the overt state is the same for both cohorts.

A long-term open label study also reported lower mortality compared with a matched cohort with 5-year survival probability was higher in patients receiving rifaximin than in controls (61% vs 13.5%, $P = 0.012$) [43].

A retrospective chart review has also reported reduced mortality in patients treated with rifaximin-α than patients treated with lactulose [44]. A recent meta-analysis of RCTs that included treatment of acute HE, covert HE and prevention of recurrence of HE concluded that treatment with rifaximin-α was associated with reduced mortality (RR: 0.64, 95% CI: 0.43**–** 0.94; [49].

These data support the plausibility of the modelled mortality benefit and indicate that the magnitude is not unreasonable

Conclusions

1. The use of minimum important difference (MID) data supports the assumption of utility gain in patients with covert hepatic encephalopathy (HE) treated with rifaximin-α. Using a published value for MID shows rifaximin-α to be a cost effective intervention.

2. The impact on both reduction in hospitalisations and length of inpatient stay seen when treating HE patients in the UK with rifaximin-α shows that rifaximin-α is at the very least cost-effective, if not cost saving, when used as part of routine care for patients with recurrent overt HE in the UK.

3. Analysis of Hospital Episode Statistics supports the contention that the effect that rifaximin-α has on improving hospital bed stay was not significantly affected by NHS efficiency targets or changes in overall bed stay policies

4. Rifaximin-α has long term data to support its clinical use beyond 6 months to reduce recurrence of overt episodes and has the potential to have a positive effect on the mortality of HE patients

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Appendix A Hospital Episode Statistics, 2010-11, 2011-12, 2012-13

The NHS in England and Wales has taken action in the last 10 years to reduce hospital bed stay as an efficiency improvement. This activity has led to hospital bed stay reductions in the NHS over a sustained period.

This analysis of hospital episode statistics data was designed to examine whether these general efficiency effects had influenced the length of stay for patients with liver disease admitted to hospital during the period of the real world audits undertaken by secondary care hepatology units in NHS England & Wales.

Table 1 describes the HRG codes for hepatology related disorders.

Table 1

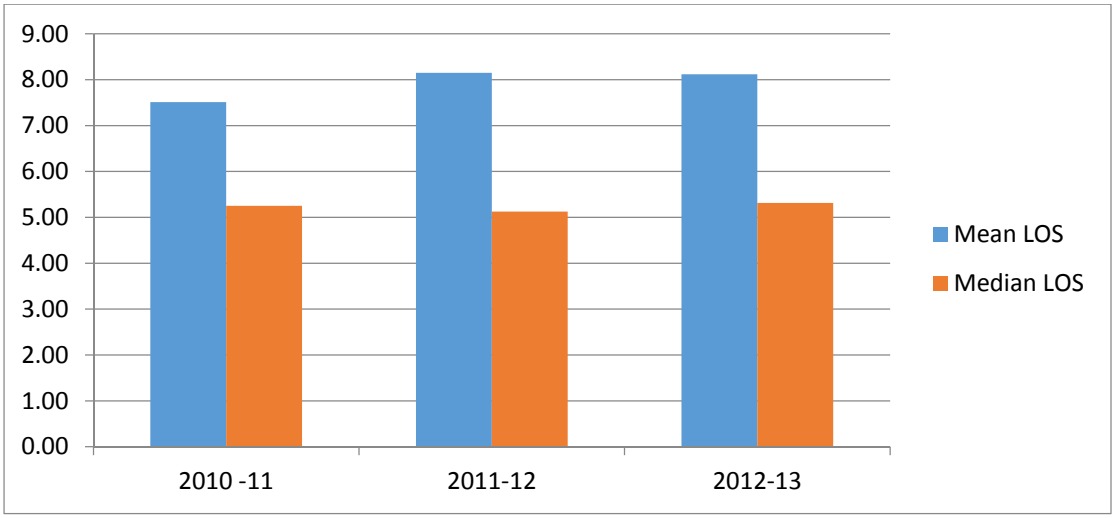
GC03A	Liver and Pancreatic Disorders category 5 with CC
GC03B	Liver and Pancreatic Disorders category 5 without CC
GC06A	Liver and Pancreatic Disorders category 2 with Major CC
GC06B	Liver and Pancreatic Disorders category 2 with Intermediate CC
GC06C	Liver and Pancreatic Disorders category 2 without CC
GC07A	Liver and Pancreatic Disorders category 1 with Major CC
GC07B	Liver and Pancreatic Disorders category 1 with Intermediate CC
GC07C	Liver and Pancreatic Disorders category 1 without CC
GC08A	Liver Disorders Category 6 with Major CC
GC08B	Liver Disorders Category 6 without Major CC
GC10A	Liver Disorders Category 4 with Major CC
GC10B	Liver Disorders Category 4 with Intermediate CC
GC10C	Liver Disorders Category 4 without CC
GC13A	Liver Disorders Category 3 with Major CC
GC13B	Liver Disorders Category 3 with Intermediate CC
GC13C	Liver Disorders Category 3 without CC

These codes describe a variety of severity and whether the condition is with or without co-morbid conditions. It should be noted that as there are no specific codes for hepatic encephalopathy, thus all codes that involve treatment of liver conditions have been included.

Annual data was analysed from the period just prior to the audits (2010) to end period of the audits presented to the Committee (2013)

Figure 1 shows the mean and median length of stay on an annualised basis for these codes

Figure 1 Length of Stay for Patients with HRG codes for Hepatology in NHS England & Wales between 2010 and 2013



Years	Mean LOS	Median LOS
2010 -11	7.51	5.25
2011-12	8.15	5.13
2012-13	8.12	5.31

This analysis simply demonstrates that there is not decrease in overall hospital length of stay for patients admitted to the hepatology clinical speciality in the period of the real world audits.

Reference for Appendix A

http://www.hscic.gov.uk/hes

Appendix B Quality of Life in Liver Disease

In a recent review of Health related quality of life (QoL) in patients with advanced liver disease, the authors reported that studies of patients with chronic liver disease have consistently shown that QOL is significantly impaired and that patients with cirrhosis have lower QoL than non-cirrhotic patients when measured by either CLDQ or SF-36 [1]. Patients with more severe disease as characterized by the Child-Pugh Score or Model for End stage Liver Disease (MELD) have poorer QoL [1]. Decompensation of liver disease is also associated with poorer QoL [2].

In their 2012 review of QoL in patients with hepatic encephalopathy, Bianchi et al [3] identified seven studies they classified as 'principal'; these are summarized in Table 1 (below).It is interesting to note that in the study by Marchesini et al [4] a significant number of patients also failed to complete the SF-36 assessment, an experience echoed in the RFHE 3001 study instrument. Overall, patients with HE had worse QoL than those without [5, 6]. In addition, patients with MHE also have significantly impaired QoL [7, 8]

In their review from 2012, Price and Younossi [9] concluded that

> *"…impairment of HRQL does indeed correlate strongly with both overt HE and minimal [covert] HE. Additionally, treatment of overt and [covert] HE can lead to improvement of the patients' HRQL."*

In summary, patients with chronic liver disease have reduced QoL and those with decompensated disease are more affected than those without. Hepatic encephalopathy further reduces QoL, with those affected having significantly worse scores than those not affected. The majority of studies also report that patients with covert HE also have worse QoL than cirrhotic patients without covert HE. The latter point is important in the context of this appraisal, as it has been shown that patients who recover from an episode of overt hepatic encephalopathy have residual cognitive impairment [10], that is they are suffering from covert HE during the time between one overt episode and the next.

Table 1: Principal studies on the association of HE and MHE with health-related quality of life (Adapted from Bianchi et al, 2012) [3]

First author, year	N	Type of HE	Instrument	Results	Limitations
Groeneweg 1998 [11] & 2000 [12]	179	MHE	SIP	Low SIP scores, mainly in alertness, sleep and rest, fine motor skills and work, are strictly linked to the presence of MHE,	The diagnostic criteria for MHE used in the survey could lead to an overestimation of its prevalence in this specific setting
Schomerus 2001 [13]	110	MHE	FPI	Impaired working abilities owing to MHE has a major impact on blue collar workers	The prevalence of MHE was not assessed by specific tests. Higher prevalence of alcoholic cirrhosis in blue collar workers
Marchesini 2001 [4]	554	OHE, MHE	SF-36 NHP	HE affects physical aspects more than mental aspects	Patients with HE failed to complete the questionnaires, with a high rate of missing data
Arguedas 2003 [5]	160	OHE, MHE	SF-36	Overt HE impairs both physical and mental aspects, whereas MHE mainly affects mental health	Patients were transplant candidates, who are expected to have a different prevalence of comorbidities and better social and health support
Bao 2007 [14]	106	MHE	SF-36 CLDQ	SF-36 scores are lower in patients with MHE, but no differences are shown in CLDQ scores	Sample includes patients with nonalcoholic cirrhosis and subjects who do not have cirrhosis (chronic hepatitis B)
Tan 2009 [15]	62 (36)*	MHE	SIP	HRQoL remains significantly impaired at follow-up, after the resolution of MHE	Small sample of patients, many who were lost to follow-up
Wunsch 2011 [16]	77	MHE	SF-36 CLDQ	MHE does not significantly affect HRQoL in cirrhosis	Small sample of patients

*At follow-up

Abbreviations: CLDQ, Chronic Liver Disease Questionnaire; FPI, Freiburg Personality Inventory; NHP, Nottingham Health Profile; SF-36, Medical Outcome Survey Short-Form 36; SIP, Sickness Impact Profile

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Appendix C – Independent 'Real World' Audits

	Centre(s)	Date published and location	Patient no's	Duration of study	Effect on frequency of hospitalisations	Effect on length of bed stay	Cost-effectiveness impact
1.The Real World Experience of Rifaximin in Hepatic Encephalopathy	Ninewells, Dundee	October 2013 Dr Falk symposium, London 2013 – poster presentation	N=16	Combined 233 months on treatment and 203 months off treatment	The total number of admissions decreased from 2.2 per patient (range 0-11) prior to and 1 (range 0-8) after starting rifaximin (p <0.05)	Average length of stay was 7.6 nights (1-58) and 4.9 respectively (1-26) (p <0.05).	This audit shows that treatment with Rifaximin for hepatic encephalopathy reduces rate of hospital admissions. This is in keeping with results of previous studies demonstrating the cost-effectiveness of Rifaximin as a second line treatment for hepatic encephalopathy.
2.Rifaximin Treatment In Hepatic Encephalopathy – A Single Centre Experience	Bristol	October 2012 Dr Falk Symposium, Germany 2012 poster presentation	N=16 (n=12)	12 months pre-rifaximin (n=12) 6 months (n=6) and 12 months (n=4) post rifaximin	Reduced from 2.33 per patient (n=12) to 0.5 (n=6 at 6 months) and 1.25 (n=4 at 12 months)	Reduced from 2.83 per patient (n=12) to 1.78 (n=6 at 6 months) and 1.29 (n=4 at 12 months)	Despite the small numbers of patients that were included in the final analysis, our study has shown that the use of rifaximin during a six or twelve month period reduces the number of hospital admissions for hepatic encephalopathy per patient and the total LOS for each admission
3.Rifaximin for HE is Cost Effective at Reducing Emergency Hospital Admission	Newcastle	June 2013 BSG UK 2013 - poster presentation	N= 64 (n= 27)	1 year pre and post rifaximin (n=27)	The mean number of admissions was reduced from 2.7 per patient (SD= 2.4) for the year prior to treatment down to 1.8 per patient (SD = 2.9) in the year of treatment (p= <0.05)	The mean duration of inpatient admissions was reduced from 28.4 days per patient (SD= 26.3) for the year prior to treatment down to 9.4 days per patient (SD = 14.7) in the year of treatment (p= <0.05)	Taking into account the cost of one year's treatment with rifaximin the reduction in the number of emergency admissions represents a mean annual saving of £2,964 per patient
4.Rifaximin treatment in Hepatic Encephalopathy: Marked reduction in hospital admissions and hospital bed day occupancy in a District general Hospital in the UK	Bolton	May 2014 Presented as poster in DDW 2014, Chicago	N=30 (n=24)	6 months pre and post rifaximin treatment (n=24)	N=24 (median values) 2 admissions 6 months pre rifaximin (IQR 1-3, range 1-5) 1 admission (IQR 0-2, range 0-4) P<0.05	N=24 (median values) 27.5 bed days 6 months pre rifaximin (IQR 16-35.3, range 2-129) 2.5 bed days 6 months pre rifaximin (IQR 0-23.5, range 0-55) P<0.05	Significant reduction in the median number of hospital admissions and bed day occupancy after commencing rifaximin treatment This study demonstrates that rifaximin treatment in patients with HE, secondary to chronic liver disease, produced a marked reduction in hospital admissions and hospital bed day occupancy with major cost savings
5.Rifaximin is efficacious in the treatment of chronic overt hepatic encephalopathy: a UK Liver multi-centre experience	Kings, Newcastle, Portsmouth, Liverpool	June 2014 Accepted at BSG UK 2014 – oral presentation	N= 170 (n=73)	3 months pre and post treatment (n=73)	Admission data available for 143/170 (84%) patients with a total of 444 admissions in the 3 months prior to therapy (average admission length 23+/-25 days). The hospitalization rate per patient fell significantly from 2.7±3.2 to 1.0±1.8 admissions in the 3 months following initiation of therapy (p<0.0001)		Rifaximin significantly reduced both hospital re-admission rates after 3 months treatment, impacting significantly on the NHS resource burden of HE, and reduced overall liver disease severity raising the possibility that its therapeutic effect may extend beyond reducing gut ammonia production
6.Rifaximin – use in preventing recurrent hepatic encephalopathy in Portsmouth	Portsmouth	In progress Submitted to BASL 2014	N=42 (N=16)	Post treatment – 3 months 26 (62%) 6 months 16 (38%) 12 months 12 (26%)	N=16 (at least 6 months treatment) Pre-rifaximin 25 admissions 3 months -2 admissions 6 months – 11 admissions 12 months - 20 admissions Overall 14 admissions saved at 6 months	N=16 (at least 6 months treatment) Pre-rifaximin 233 bed days 3 months 28 bed days 6 months 143 bed days 12 months 158 bed days Overall 90 days saved at 6 months	In 6 month cohort (16 patients) – 90 fewer bed days compared to 6 months pre-Rifaximin Average 5.6 bed days per patient Total saving of £1528.80 per patient Also 14 fewer admissions in 6 months Rifaximin is likely to offer value for money as a means of reducing hospital admissions in this patient group

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6. Real World' Experience of Rifaximin for Hepatic Encephalopathy: Effective maintenance of remission and Reduced Hospital Admissions in a Large Secondary care Cohort. Preedy H, Fowell A, Aspinall R. Department of Gastroenterology and Hepatology Portsmouth Hospitals NHS Trust. Queen Alexandra Hospital, Portsmouth UK. Poster presented at BASL September 2014