Response to the questions raised by the ERG on 4th December 2014.

Q1 The ERG notes that the ICERs reported in the written submission (for example, base case with a lifetime horizon = £17,810) differ from those produced by the model provided to NICE on 11th November (for example, base case with a lifetime horizon = £17,834). They also note that the ICERs in that model match those in the previous written submission (for the meeting in April 2014). However, neither of the 2 models supplied with your initial clarification response (received by NICE on 2nd December) appear to match the current written submission, the current economic model (as received 11th November), or the previous written submission.

- *Which ICERs are correct?*
- *If those in the written submission are correct, what changes to the model are required? Or which version of the model should the ERG use in its review?*

Response: To clarify the corrected version of the model is the "resubmission" submission document that was previously attached with the "November 11th" document. We have reattached this model to the covering e-mail.

As stated in our response on 2nd October the error was due to:

- a rounding error which can be found in Parameters!Q204. The value entered here can change the ICER slightly depending if it is manually in put or not. The figure to be inserted here is the RIF increment to 3 decimal places (0.106) and not 0.10602
- a displacement of Kind's (1999) age-related utility ratio adjustment. In the parameters tab you will notice that when comparing the two documents there is a copy and paste error in column J starting at cell J65 and ending at cell J72. This is rectified in the "resubmission" titled document.

When inputting the base case options in the first tab of the resubmission document this now aligns this lifetime ICER with that of previous submissions and gives a value of £17,834.

Therefore in the "resubmission" zip file model, setting the derivation of utility option to 7 instead of 8 in 'Options for analysis & results'!B22 (which is the base case CLDQ derived utility values) the lifetime ICER is corrected to read £17,834 rather than the mistaken value of £17,810.

Q2 In addition, the ERG has requested that we also raise the following further queries for clarification.

2.1

The ERG notes that the estimated mean bed days per patient per year before and after rifaximin for Dundee differ in different parts of the submission (see Table 1 Below). Please clarify these discrepancies.

Table 1

Data source	*N in analysis*	*Before rifaximin, mean bed days per patient per year (SD, where available)*	*After rifaximin, mean bed days per patient per year (SD, where available)*	*Mean difference*
Meta-analysis data (further submission Table 7)	*16*	*16.2 (17.59)*	*3.5 (17.59)*	*12.7*
Preliminary descriptive analysis (further submission Table 5)	*16*	*13.8*	*4.6*	*9.1*

Response: The preliminary descriptive analysis (See Appendix A, below) referred to in table 5 was carried out in August 2014 and sent to NICE during the suspension of the FAD.

Following the request for a further submission from NICE a meta-analysis was undertaken in October (Table 6, 7 et seq in the submission) and the results from this meta-analysis were used as inputs in the model.

2.2

The ERG notes that bed days data presented in the original sources for the Bolton and Dundee centres were per admission rather than per patient per year. The submission details that data were 'annualised' for these two centres, but the ERG is unclear from the information in the

submission if this means that these data were transformed to mean number of bed days per patient per year or transformed to mean number of bed days per patient per year per admission for use in the meta-analysis.

Response: The meta analysis looks at bed days per patient per year.

2.3
Please provide a justification for the choice to assume a constant event rate when annualising data for use in the meta-analysis.

Response: Norgine alerted NICE to the fact that our analysis of real world data was based only on those audits published and used data in the public domain. Without access to the raw data from the real world audits a constant event rate seemed a reasonable default assumption. As we noted in our e-mail to NICE on 26th November we have been made aware of a larger, independent, multi-centre analysis of UK 'real world data' that has been submitted to the European Association for Study of the Liver (EASL) for their next meeting (April 2015). We have been given permission by the lead author (Dr Mark Hudson, Consultant Hepatologist, Freeman Hospital Newcastle, who is also the current Chair of the British Association for Studies of the Liver, BASL) to share the abstract with you (academic in confidence), to ensure a complete review of available information by the ERG and Committee. We have again attached the abstract for your information and we would suggest that you contact Dr Hudson direct.

[redacted] attached and sent to NICE on 26th November):

[redacted]

[redacted]

Please provide details about any searches, databases searched and selection criteria used to identify the 6 RWD audits listed in Appendix C of the submission.

Response: No formal search was undertaken. The absence of a decision from NICE and the limited number of current effective treatment options for patients with HE has resulted in a number of hepatology centres seeking to gain local access to rifaximin-α as a treatment option for their patients. These clinicians independently carried out local 'real world' audits to investigate the potential for service efficiencies and resource reduction that may be associated with the introduction of rifaximin-α and the data have subsequently been used to support both local and regional formulary and prescribing decisions.

These audits were identified as key outputs from gastroenterology & hepatology academic meetings

Appendix A – Preliminary descriptive analysis.

Real world data -*Estimation of the impact of treatment with rifaximin-α on hospital bed utilisation.*

By Craig Currie, Professor of Applied Pharmacoepidemiology. August 2014

BACKGROUND: A number of audits have been produced from NHS hospitals (attached in the electronic version of this document.) However, these were not standardised in any way. They were all analyses of data from people treated with rifaximin-α before and after their exposure to the drug. In effect, they each had internal controls. An exercise was carried out to produce an amalgam of these data in order to determine the magnitude of the impact on NHS hospital utilisation of rifaximin-α treatment. From the audits available and appended below, four were suitable for a combined analysis: Dundee, Bristol, Newcastle and Bolton. Data were available from a total of 120 patients (Table); with over-representation from Newcastle (64 patients).

RESULTS: These data are interesting and compelling (Table A). They illustrate that in independent audits (combined reduction of 46%), rifaximin-α had a consistent impact on not only reducing the risk of hospital admission, but that the drug also reduced hospital length of stay when admissions occurred (combined reduction 45%). These two factors have a combined impact on hospital bed utilisation. The overall reduction in bed utilisation of combining reduced admission and reduced length of stay was a 70% reduction in hospital bed utilisation, and this ranged from 59% to 90% across the four hospital audits.

CONCLUSION: whilst these audits are small and diverse in nature, they formulate a consistent story of the beneficial impact of rifaximin-α on reducing NHS resources in terms of hospital bed utilisation.

Table A: 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

Title	Location	Date published location	Patient no's	Duration of study	Effect on frequency of hospitalisations	Effect on length of bed stay	Cost-effectiveness impact	Attachment
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.	The Real World Experience of Rifaxim
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	Rifaximin Treatment in Hepatic Encephalop

							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	Rifaximin for Hepatic Encephalopathy is Co

4.Rifaximin treatment in HE: 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	marked reduction in hospital admissions a