Hi Chris,

Thank you for the invitation to comment on the ACD and evaluation report for the telbivudine appraisal. Comments from the ERG are given below:

Clinical effectiveness

1. There is only one small error - in section 3.2, p.5 of the ACD, it states there were 1397 patients in the Globe study. This should be 1367.

Cost effectiveness

2. Section 3.7 (p 8) of the document states "No comparisons were made in the seroconversion model of telbivudine against adefovir dipivoxil or lamivudine as separate treatments." - not strictly true. The MS did not present any comparisons of telbivudine against other agents (all comparisons were, incorrectly, made against best supportive care). However such comparisons could be made (and were done by the ERG, see Table 5 of the ERG report, column 5 headed "compared with next best strategy"). The current wording suggests that the MS did not model lamivudine as monotherapy, which is not correct.

3. Section 3.9 (p 8) of the document states "Following the identification of errors in the manufacturer's original economic model by the ERG, amended base-case analyses were presented." - this should probably be clearer that the errors were only in the viral load model and results were only re-submitted for the viral load model.

4. Section 3.11 (p 9) of the document reports the ICERs from the seroconversion model using the comparisons reported by the manufacturer only - i.e. the incorrect analysis comparing all strategies against best supportive care. You may want to mention that the ERG conducted an analyses where options were eliminated using dominance/ extended dominance. This gives an ICER of £24,277 for telbivudine followed by adefovir when compared with telbivudine (rather than £15,684, as reported in MS (and ACD), for telbivudine followed by adefovir when compared with best supportive care).

5. Section 3.14 (p 11) of the document states "The ERG noted discrepancies in the calibration factors in the risk equations used for the compensated cirrhosis and hepatocellular carcinoma states in the original and resubmitted economic models and those listed in the appendices to the manufacturer's submission" - it should be clearer that this only applies to the viral load model.

6. Section 3.14 (p 11) of the document states "In general, the ERG noted that the manufacturer's submission did not provide summaries of the model parameters, " - this is not strictly true. The main body of the MS did not contain details of model parameters. However the parameters were documented in appendices to the MS.

7. Section 3.15 (p 12) of the document states "The cumulative effects of varying these parameters gave an ICER of £8,400 per additional QALY gained." - it should be stated that this ICER was calculated for telbivudine followed by adefovir compared with lamivudine followed by adefovir.

8. Section 3.16 (p 12) of the document states "The ERG conducted a PSA using the viral load model with a 'non-informative prior' of 0.0 only; replacing constant health state utilities with non-constant age-specific utilities and applying model calibration factors for risk of advanced liver disease." - it should be clearer what calibration factors were used. We replaced the values in the electronic model with those reported in appendix C of the manufacturer's submission.

9. Section 3.16 (p 12) of the document states "The ERG also conducted a PSA using the seroconversion model; the results differed from the manufacturer's analysis in that over a cost effectiveness threshold of £20,000 to £25,000 per additional QALY, the optimal strategy in the ERG's analysis was lamivudine followed by adefovir whilst telbivudine was the optimal strategy in the manufacturer's PSA." - the range of WTP over which lamivudine followed by adefovir was optimal, as stated in the ERG report, was £22,000 to £24,000. You may also want to state that the strategy of telbivudine followed by adefovir remained the optimal strategy at higher values of WTP (i.e. over £25,000).

10. Section 4.5 (p 15) of the document states "The Committee was advised by the clinical specialists that estimates of the efficacy of telbivudine in this subgroup were subject to some uncertainty because they were based on a post-hoc analysis, and randomisation was not stratified according to serum ALT levels." - this is not strictly correct. Randomisation was stratified by ALT, but not at 2 X ULN. According to the MS randomisation (section 5.3.1, page 29) "Treatment assignments were stratified by HBeAg status (positive or negative) and by serum ALT level (above or below 2.5 times the upper limit of normal)."

Kind regards,