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[redacted]

November 28, 2008

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Dear Mr Boysen

Single Technology Appraisal – Tenofovir for the treatment of chronic hepatitis B

Many thanks for your continued correspondence regarding the above appraisal. We have responded to all the questions from the Evidence Review Group (SHTAC) in the below tables. Please do not hesitate to contact us if you have further questions. Furthermore, we would be happy to attend a teleconference/web conference or meeting with SHTAC to demonstrate use of the model/functionality if this would be more efficient than written explanations.

Despite methodological complexities, I am sure you will agree that Tenofovir is intuitively cost effective compared to other nucleos(t)ides with a lower unit cost, lower resistance and greater efficacy than other drugs in its class.

Yours sincerely,

[redacted]

[redacted]

Section A: Clarifications of the effectiveness data

Q. number	Question.	Response including location of additional data/amends.
A1.1	Please provide a copy of the full search strategy. Currently there is no indication of whether free text and/or subject index headings (e.g. MeSH in Medline) terms were used. If possible please can the strategy as run be supplied (e.g. that shows the number of hits generated by each line of the strategy). This will enable us to check the results of the search.	The pivotal Medline search was conducted on 31st August 2007. The search strategy is shown in Response Appendix A. In total, Pubmed (Medline) searches identified 1057 publications. The MeSH term for "Hepatitis B" was included in the search strategy.
A1.2	Please specify the host system used for the Medline search (e.g. Ovid)	The host system for the Medline search was PubMed.
A1.3	Please clarify exactly which years were searched?	The searches were conducted on the 31st August 2007 and this was the end date for all the searches. The searches on entecavir, telbivudine and tenofovir were not limited by start date. Searches for adefovir and lamivudine were conducted from 1st July 2004 onwards, as previous systematic reviews had been conducted for these agents up to this point.
A1.4	Were Embase, the Cochrane Central Register of Controlled Trials and MEIP (Medline in Process) searched?	No, these databases were not searched. MEDLINE/PubMed and the Cochrane library (Database of Abstracts of Reviews of Effects (DARE), Cochrane Database of Systematic Reviews, Cochrane Methodology Register, Health Technology Assessment Database and NHS Economic Evaluation Database) were searched.
A1.5	Were any search filters used to retrieve RCTs or cost effectiveness studies?	Search filters were not used to retrieve RCTs or cost effectiveness studies.
A1.6	We note that the database searches are current to 31st August 2007. Was an identical update search run on all the databases?	All searches ended on the 31st August 2007 and we did not replicate any searches after this date.
A1.7	The 'NewDrugFile' database is mentioned. Please specify whether the version used is hosted by Promedis	The version of the NewDrugFile database used is hosted by Promedis.
A1.8	Were ongoing trial databases searched (i.e. UKCRN, clinical trials.gov, controlled clinical	These databases were not searched. However, we did search manufacturers' websites and the proceedings of a key conference (AASLD 2007) to identify ongoing trials.

	trials.com in addition to NewDrugFile?)	
A2.1	In Figure 1 (Section 6.1, page 23) it reports that of 170 publications that met the criteria for the systematic review, there were 122 papers describing non-randomised studies, of which 46 non-randomised trials met the inclusion criteria for the systematic review. Does this mean that 76/122 studies were excluded, despite them meeting the criteria for the systematic review? Were the 46 non-randomised trials reported in a total of 122 papers?	We acknowledge that the figures were confusing. We have re-drawn Figure 1 (Section 6.1, page 23) and added more detail to clarify study identification for the systematic review. The new figure is shown in Response Appendix B.
A2.2	Please can you supply full bibliographical details of the 46 non-randomised trials included in the systematic review.	Full bibliographical details of the 46 non-randomised trials included in the systematic review are shown in Response Appendix C.
A2.3	Please specify whether any of the 170 publications meeting the inclusion criteria were duplicates.	There were no exact duplications within the 170 publications meeting the inclusion criteria (i.e. the same paper did not appear twice), however there were multiple publications (i.e. different papers relating to the same study) of some studies from different sources.
A2.4	In Figure 1 (page 23) an asterisk appears in four of the boxes in the lower left hand corner. To what is this asterisk referring?	The GLOBE study was included as two trials: one on HBeAg-positive patients and one on HBeAg-negative patients.
A2.5	On page 23 (section 6.1) it is mentioned that there are 7 RCTs of tenofovir, but in table 6.2.1 there are 8 listed. Was this a typographical error? In which case should there be 53 RCTs in total?	Fifty-two RCTs were identified by the systematic review (excluding the 25 RCTs on adefovir and lamivudine identified by the previous systematic review) and 7 of these RCTs were on tenofovir as stated. The 8th study in Table 6.2.1 is study 0121, this is an ongoing study of tenofovir identified through Gilead representatives, for which there is currently no available data. It was included in Table 6.2.1 for completeness only. We will remove this trial from Table 6.2.1 to avoid confusion.
A2.6	Of the 52 RCTs that met the inclusion criteria for the wider systematic review, 23 met the criteria for the MTC. Please can you supply full bibliographical details and reasons for excluding the 29 that did not meet the criteria for the MTC.	Full bibliographical details and reasons for excluding the 29 trials that did not meet the criteria for the MTC are given in Response Appendix D.
A2.7	Page 81 (6.10.1.4): please clarify why the section of resistance surveillance in weeks 0-48 of studies 01202 and 0103 is marked as CIC, when the information has been or is due to be presented at EASL conference(s)?	We apologise, this was marked in error and the submission has been amended accordingly.

A3.1	On page 60 (Section 6.6.2) it is reported that 13 trials met the inclusion criteria for the MTC. This contradicts the figure of 23 given in Figure 1 (Section 6.1, page 23) and also given in Appendix 4. We presume this is a typographical error?	This confusion relates to whether we were looking at all subgroups (23 trials) or those relating to particular subgroups such as HBeAg-positive treatment naive patients (13 trials). This paragraph has been amended and now reads; A total of 23 RCTs met the narrower inclusion criteria for the meta-analysis (Figure 1, Section 6.1), (13, 19, 20, 43, 44, 74, 76, 79, 87-104) of which 13 were on treatment-naïve patients with HBeAg-positive CHB (19, 43, 44, 76, 79, 87-94). Four RCTs met the criteria for the HBeAg-negative treatment-naïve subgroup (13, 20, 43, 74); five met the criteria for the HBeAg-positive lamivudine-resistant subgroup (95-103); and one met the criteria for the HBeAg-negative lamivudine-resistant subgroup (104).
A3.2	Was there any critical appraisal of the studies included in the mixed treatment comparison? If so please can you supply details.	No critical appraisal of individual trials was conducted. However all trials included in the meta-analysis were randomised and controlled. Tenofovir trials were critically appraised as part of the submission, (Table 12, Section 6.3.6).
A3.3	The description of the inclusion criteria for the MTC is inconsistent between the main submission and Appendix 4. In particular on page 31 of Appendix 4 it says that 'HBeAg-positive, lamivudine-resistant/refractory with/without HIV co-infection' were eligible. This isn't mentioned in the main submission document. Please can you clarify what you mean by 'with/without', and why this only applied to this one subgroup? We presume that it was for sensitivity analysis purposes, but would like clarification.	The pre-specified inclusion criteria for the meta-analysis excluded studies in which ≥50% of the total cohort were co-infected with HIV. The analysis described as "HBeAg-positive, lamivudine-resistant/refractory with/without HIV co-infection" on page 31 of the appendices and as "Results for HBeAg-positive lamivudine-refractory HIV co-infected patients"[1] on page 64 of the main submission included those studies in which ≥50% of patients had HIV co-infection (but which met all other inclusion criteria) in addition to those trials that had no (or fewer) patients co-infected with HIV. The analysis that included trials on patients with HIV co-infection and those on monoinfected patients was a sensitivity analysis of the meta-analysis, although its results were used in the economic model.
A3.4	In Appendix 4 we presume that no table of the baseline characteristics / table of results for the lamivudine-refractory patients (similar to the tables for nucleoside naïve patients – Tables 5 and 6) was not supplied because there were no RCTs of tenofovir in this patient group and therefore full results of this analysis are not reported. We assume the same for HBeAg negative patients in nucleoside/nucleotide naïve	This is correct. However, brief details and baseline characteristics of the studies included in these meta-analyses are shown in Tables 7-10 of Appendix 4.

[1] In the amended version of the report, we have amended this sentence to: "Results for HBeAg-positive lamivudine-refractory patients with or without HIV co-infection" for consistency and clarity.

	patients as an MTC was not possible. Please can you confirm that this is the case.	

Section B: Economic analysis

Q. number	Question.	Response including location of additional data/amends.
B1	In Section 7.1.1 it is stated that two cost-effectiveness evaluations were included in the review of cost-effectiveness, out of a total of 170 included publications. As the searching for clinical and cost-effectiveness studies appears to be combined please can clarification be given as to where these two studies fit in to Figure 1 in section 6.1. In Figure 1 the 170 publications are described as either being RCTs or non-randomised studies, but no mention is made of cost-effectiveness studies (unless these are counted as being non-randomised studies?)	Cost-effectiveness studies were excluded from the systematic review of clinical outcomes, as per the inclusion criteria, and are not in the 170 included publications. However, for the later section of the STA form, which asks for a review of cost-effectiveness studies, we separately scrutinised all hits from the original systematic review to see if any were cost-effectiveness trials. No cost-effectiveness studies were found as part of this search. Nonetheless, at a later date, two cost-effectiveness studies were published as abstracts and we were made aware of them through contact with Gilead representatives and conference proceedings, we therefore included these studies in section 7.1.2 for completeness.
B2.	In the model, the same mean age at start of treatment is assumed for HBeAg positive and HBeAg negative patients. However, Appendix 7 of the MS quotes figures for the "global population with CHB", drawn from a review on the natural history of CHB by Fattovich, giving a median age of 31 for HBeAg positive patients and of 40 for HBeAg negative patients. The Fattovich review also suggests that a larger proportion of HBeAg negative patients will have compensated cirrhosis (compared with HBeAg positive patients).	The same time horizon (or average age) was used for both HBeAg-positive and HBeAg-negative patients for simplicity and to ensure that the two subgroups could be compared fairly without the added complication of having the two analyses using different time horizons. Furthermore, there is no evidence from the London clinic audit that there is any difference in average age between HBeAg-positive and HBeAg-negative patients when patients who are immunotolerant and those who have undergone HBeAg or HBsAg seroconversion are excluded. Furthermore, sensitivity analyses demonstrate that assuming different ages for the two patient groups would have had no effect on the conclusions. Based on the Scottish life tables used in the analysis, the life expectancy of a cohort of 31-year old patients (the average for HBeAg-positive patients based on global data (110)) of whom 62.7% are male is 47 years; the results for HBeAg-positive patients of this age are shown in Table 45 and are only slightly lower than those in the base case analysis. Similarly, the life expectancy of a cohort of 40-year old patients (the average for HBeAg-negative patients based on global data (110)) of whom 62.7% are male is 38 years; at this life expectancy, tenofovir then lamivudine would cost £7,430/QALY gained relative to BSC.
B2.a	Please provide a rationale for assuming the same starting age (or alternatively the same time horizon) for both groups of patients?	
B2.b	Were there additional data from audit of patients attending the London hepatology clinic that would support this assumption?	[redacted]

		[redacted]
B2.c	Did the clinicians providing expert advice support the assumption, included in a footnote to Table 30 in the MS, that 50% of all patients with compensated cirrhosis were HBeAg negative?	This assumption was not validated by clinicians. However it is unlikely to have a big impact on results due to the small proportion of patients assumed to be cirrhotic at baseline.
B3	Please provide a rationale for using constant values for all-cause mortality, rather than age-specific values?	To incorporate age-specific mortality we would need to re-generate all the transition probabilities for each cycle of the model. Due to the large number of transition probability tables it was felt that attempting to model age-specific mortality would add unnecessary complexities (there are currently 56 transition probability tables, if we had to reproduce these tables for each cycle in the model we would have hundreds of tables to model. Further to this the computational power required to generate these tables in PSA would result in very limited functionality).
B4	Please explain how you derived the figure of 1.07% annual mortality for males and 1.09% annual mortality for women? These do not seem to correspond to the quoted life expectancies at age 38, from Scottish life tables, of 38.5 years (male) and 42.6 years (female). The ERG estimated annual mortality rates from these life expectancies (using the DEALE method) would be 2.60% (risk = 2.56%) for men and 2.35% (risk = 2.32%) for women.	The annual mortality rates are taken from the General Register Office for Scotland (See Response Appendix E, Reference 1). This table provides the total population and total number of deaths in Scotland during 2006, which are used to estimate an average annual rate of death across all age groups. We have performed additional analysis using the ERG estimations of annual mortality (Appendix E, Table 1 and Table 2) and although all costs and QALYs presented for each scenario decreased, the relative differences do not change dramatically and all of the conclusions reached remain unchanged.
B5	Please clarify whether there are any assumptions (implicit or explicit) in the model, regarding regression from compensated cirrhosis to CHB/ viral suppression?	In the base case analysis, the model explicitly assumed that there was a 0% chance of cirrhosis regressing, such that no patients were assumed to move from compensated cirrhosis to either active CHB or to viral suppression, as stated on page 84 of the appendices and on page 116 of the text. However, this assumption was varied in sensitivity analyses (row labelled “Assuming that 5% of treated HBV DNA-negative cirrhotic patients show regression of cirrhosis and move back to viral suppression each year “ in Tables 45 and 47), which demonstrated that this assumption had minimal effect on the results.

[2] The average age for the total cohort of HBsAg-positive patients that was used in the submission is increased slightly by the group of patients who have undergone HBeAg seroconversion.

B5.a	Page 116 of the MS states that patients could not revert from compensated cirrhosis to active CHB or viral suppression, regardless of viral load or treatment. However the arrows between active CHB/ VS and CC/ CC with undetectable HBV DNA are two headed (suggesting movements in both directions and contradicting the statement on Page 116) – see Figure 1 below. Please clarify which approach was used in the model?	Figure 5 has double-headed arrows between compensated cirrhosis and active CHB/viral suppression to indicate that the model structure allows for the possibility that patients could move from compensated cirrhosis to VS/active CHB. However, in the base case analysis, these probabilities were set to zero, as stated on page 116 (See cells E30 & E31 on the Efficacy (2) sheet of the model and cells C29:L29, C30:L30, C34:L34, C35:L35, C60:L60, C61:L61, C65:L65 and C66:L66 on the TP calc sheet for these values). We apologise for any confusion caused.
B5.b	Please could you state whether patients who achieve HBeAg seroconversion from a compensated cirrhosis state (either compensated cirrhosis with detectable HBV DNA or compensated cirrhosis with less than 300 copies per mL HBV DNA) move to a compensated cirrhosis state or to active CHB when reactivating disease – i.e. does the model implicitly assume that HBeAg seroconversion is associated with regression of cirrhosis (by allowing previously cirrhotic patients to enter the CHB state) or does the model contain memory of seroconverted patients previous health state(s)?	We have looked into this issue further and have realized that there was a discrepancy between the model and the described methodology, in that the model assumed that 0% of patients could move from the HBeAg seroconverted state to compensated cirrhosis. We have corrected this error and rerun the base case results, which are shown in Response Appendix E Table 3 and Table 4. Correcting this error has no effect on the conclusions and has only a small impact on ICERs for HBeAg-positive patients. Furthermore, it has no impact on outcomes for HBeAg-negative patients as they cannot enter the HBeAg seroconverted disease state. The model now assumes that patients who experience disease reactivation after HBeAg seroconversion may move to one of four states: • HBeAg-positive active CHB • HBeAg-negative active CHB • HBeAg-positive compensated cirrhosis with detectable HBV DNA • HBeAg-negative compensated cirrhosis with detectable HBV DNA This assumption matches the data inputs presented in Appendix 9 and the assumptions/model outline described in Section 7.2.6, page 98, of the submission. Due to the Markovian assumption, it is not possible to track the history of patients through the model without using tunnel states; subsequently, all patients in the HBeAg seroconversion state are assumed to be identical, regardless of whether or not they had previously had cirrhosis. The probability of making one of these four transitions is therefore the same for patients who were cirrhotic when they underwent HBeAg-seroconversion as for patients who have not yet developed cirrhosis. However, this simplification will have little/no effect on the total costs or benefits for a large cohort of patients of whom only a minority will have seroconverted from the cirrhotic state.
B5.c	If the model allows previously cirrhotic patients (who have seroconverted) to enter the CHB state on reactivation of disease, was this assumption based on observed data and/ or was this assumption clinically validated?	The corrected version of the model assumes that patients in the HBeAg seroconverted state may move directly to the compensated cirrhosis state is in line with evidence from published natural history studies (116, 125-127).

B6	Please can you provide a rationale for using data on the development of resistance to combination treatment from an abstract (Sung et al. J Hepatol. 2003;38(Suppl 2):25-6) given that the trial has now been reported in a full journal publication (Sung JJY, Lai JY, Zeuzem S, Chow WC, Heathcote EJ, Perrillo RP, et al. Lamivudine compared with lamivudine and adefovir dipivoxil for the treatment of HBeAg-positive chronic hepatitis B. J Heptatol 2008;48:728-735), including up to two years of data?	The full journal article was not published until after the search date of our systematic review and consequently we were not aware of it at the time the submission was made. Hence data from the abstract was used.
B7	The section on utilities (7.2.8.3) refers to a poster by Ossa and colleagues and to a published paper by Levy and colleagues. Values used in model are taken from Ossa and colleagues rather than from the fully published study, but there is no discussion of the reason for this choice or any effect this may have on the model results. Could you supply the rationale for adopting the health state valuations from Ossa and colleagues, rather than the UK-specific values presented by Levy and colleagues?	Since utilities varied between countries and as it is appropriate to use health state valuations taken from the UK within UK economic evaluations (where available), we used the standard gamble valuations for the UK participants in the analysis instead of the averages across the six countries used in the study. Levy et al present only mean utilities specific to UK participants, which they present both as utilities adjusted for age and sex (Table 5 of the Levy paper) and as unadjusted utilities (Figure I). However, the standard errors or deviations around the valuations provided by the UK sample are not given in the full paper. Consequently, it was not possible to obtain data on the sampling distribution of utility values from the Levy paper and values were therefore taken from the poster by Ossa et al. The unadjusted utility values from Table 3 of the poster approximately correspond to the unadjusted utility values shown in Figure I of the paper by Levy et al (based on reading off the figure by eye), although (as would be expected) they do differ from the values shown in Table 5 of the Levy paper, which are adjusted for age and sex.
B8	There appear to be inconsistencies between Table 37 and Table 38 in the submission (and between Table 37 and the submitted electronic model). The inconsistencies are as follows: • The row labels in Table 37 are consistent with Table 38. However many of the total cost and total QALY values are not consistent between the two tables. • The row labels and content of Table 38 are consistent with the submitted electronic model. It appears that there has been an error	The electronic copy of the model contains the correct values. It appears that the strategies listed in the first column of Table 37 in the submission are in the wrong order. See Response Appendix E for the amended Table 37.

	populating Table 37 – can you confirm that this is the case and that Table 38, and the submitted electronic model, contain the correct values?	
B9	The cost effectiveness acceptability curves presented in Figure 15 of the MS, for the HBeAg negative population, do not appear to be correct (or consistent with data for the deterministic base case presented in Table 38). The ERG have re-run this analysis using the submitted electronic model, deriving CEACs and a cost effectiveness acceptability frontier as shown in Figure 2 below (the cost effectiveness acceptability frontier is shown by the heavy black curves, with associated labels indicating the treatment strategy yielding the maximum average net benefit at each willingness to pay threshold).	
B9.a	Please can you confirm whether the CEACs and cost effectiveness acceptability frontier derived from the PSA conducted for the submission are correctly presented in Figure 15 of the MS or whether they are similar to those presented in Figure 2 above?	Thank you for drawing this discrepancy to our attention. We agree that the figures generated by the ERG are correct. Due to the complex nature and scale of the model, several versions of the model were generated to produce the required results. We therefore had a deterministic version, a probabilistic version, a version for tornado diagrams and a version for threshold analysis. Minor modifications were required to each version to generate results for the two patient subgroups (HBeAg positive and HBeAg negative). Upon review it appears that the model used to generate the PSA for the submission contained a minor error relating to two cells. However, whilst consolidating all of the above models into a single model to send to the ERG, this error was addressed resulting in the correctly working version being sent to the ERG, which differed slightly to the subsection of the submission where these sensitivity analyses were reported. This occurred in the probabilistic version only. It appears that in converting the model to consider HBeAg negative patients from HBeAg positive patients the PSA range defining the HBeAg positive patients was not correctly updated (cells I233 and H233 on the Data & References sheet). This resulted in some simulations generating a negative value in the starting state page (cell E16) which in turn resulted in the incorrect CEACs and cost effectiveness acceptability frontier submitted in the submission.
B9.b	If the analysis presented in Figure 15 of the MS is correct, can you provide a rationale for why the ERG replication of this analysis using the submitted model (presented in Figure 2 above) is so different?	

		This has already been addressed in the version of the model originally submitted and the amended probabilistic sensitivity analysis write up has been included in appendix F. It should be noted that the error only affected the probabilistic sensitivity analysis and would not result in any differences to the deterministic results or the other sensitivity analysis results presented. It should also be noted that the updated probabilistic results still show first line tenofovir is cost-effective.
B10	There appear to be errors in the calculation of the mean ICERs for "TDF then LAM" relative to other treatment strategies in Table 43 of the MS. Examination of the electronic model suggests that calculations to derive mean ICERs (in cells DY4 to ER4 on the "Simulations" sheet) are based on maximum values (derived in cells H4 to DW4 the "Simulations" sheet) rather than averages	The values calculated by the ERG are correct; the table was linking to the maximum values rather than the means. This has been corrected in the amended version of the submission. See Response Appendix F for the amended Table 43 – Please note that this table is based on the amended probabilistic results generated for B9.
B10.a	Please can you confirm that the calculation of mean ICERs presented in the MS is incorrect and that the calculations conducted by the ERG are correct?	
B10.b	The ERG have not been able to check the calculations for the HBeAg positive cohort as no spreadsheet containing the results for this cohort has been submitted and the submitted electronic model is setup to run probabilistic analysis only for HBeAg negative cohort. However, it is likely that these calculation errors also apply to the mean ICERs in Table 42 of the MS (please can you confirm)?	The ERG are correct in their observation, the same error occurred in the HBeAg positive cohort. This has been corrected in the amended version of the submission. See Response Appendix F for the amended Table 42 – Please note that this table is based on the amended probabilistic results generated for B9.
B11	When running the PSA for the submitted electronic model (which allows analysis of ten treatment strategies (BSC then BSC, LAM then TDF, TDF then LAM, TDF then TDF+LAM, TDF then TDF+LAM then ETV, LAM then BSC, LAM then ETV, LAM then	Yes, we did see these notifications when conducting PSA and such simulations were excluded from all averages presented in the report.

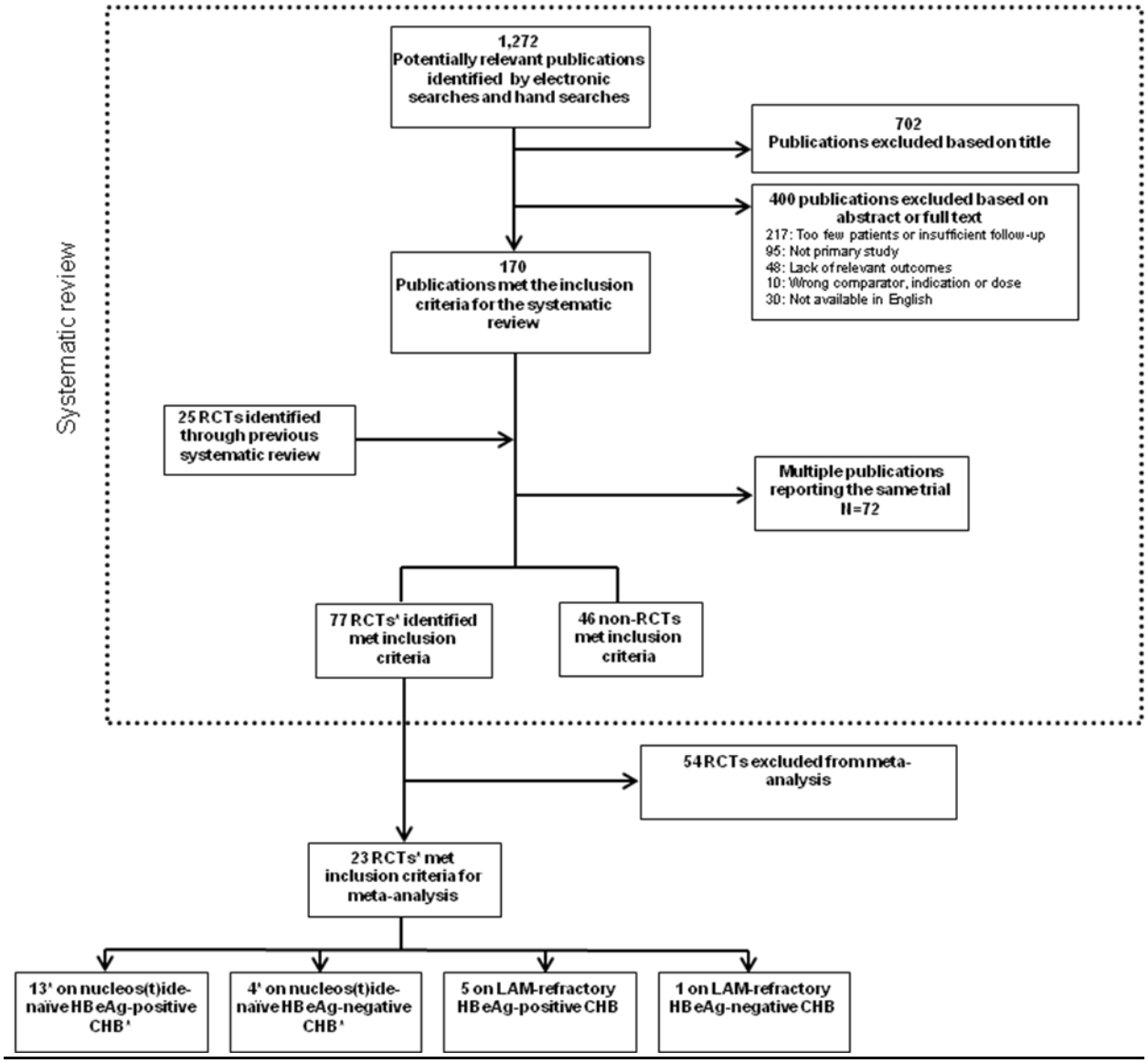
	ADV, ADV then LAM, LAM then TDF+LAM)) there appear to be errors in approximately 4% of simulations for some of the included treatment strategies (LAM then TDF, TDF then LAM, TDF then TDF+LAM, TDF then TDF+LAM then ETV, LAM then ADV, ADV then LAM, LAM then TDF+LAM). The ERG cannot investigate the cause of these errors as access to the visual basic code in the model has been password protected. All we can report is that around 4% of simulations for the above strategies have invalid values (reported as #NUM! in cells in the output area of the "Simulations" worksheet).	
B11.a	Please can you confirm whether or not you observed such errors in the output from the PSA conducted for the MS?	
B11.b	Please can you identify the cause of these errors in the electronic model submitted to NICE?	The errors in the simulations occurred when the randomly generated first year probability of HBeAg seroconversion in lamivudine resistant patients is relatively high and the randomly generated relative risk of HBeAg seroconversion in year n compared to year one is also high. In a small proportion of the simulations this scenario occurred resulting in the probability of HBeAg seroconversion in subsequent years being above 100% which subsequently caused errors in the model calculations. This error is a result of the large number of variables and complexity of the model combined with the randomness of PSA. Rather than try to adjust for these occurrences through manipulation of the data we felt it was more appropriate to remove the simulations where this error occurred.
B12	Please provide instructions for running the model / PSA and a description of what is shown on each of the Excel worksheets	An overview of the model and its functionality can be found in Response Appendix G. Further detail and/or instruction can be provided if required.
B12.a	Is it possible to run the model for a smaller number of scenarios, for example only scenarios 1-20, without access to the visual basic code?	The number of scenarios considered is defined in the visual basic code (currently this is set to 20), The ERG have been provided with an unprotected version of the model so can manually amend the number of scenarios in the visual basic code. It is possible to make this dynamic (i.e. only run for the number of scenarios defined without having to amend the code), this can be provided on request.
B12.b	Is it possible to run any of the scenarios on its own deterministically and if so	All deterministic results are generated on the scenarios sheet.

	where are the results shown?	It is possible to remove/add other scenarios to this screen by defining the required scenario in columns E:K and generating the results by clicking on the generate scenarios button. The deterministic results can be reviewed individually on the results screen. This sheet presents the results for the selected scenarios generated on the scenarios sheet.

Response appendix A: PubMed search strategy

Search no.	Terms
#1	Tenofovir OR Viread
#2	Telbivudine OR Sebivo OR Tyzeka
#3	Entecavir OR Baraclude
#4	#1 OR #2 OR #3
#5	"hepatitis b"[MeSH Terms] OR "hepatitis b"[All Fields]
#6	HBV OR CHB
#7	#5 OR #6
#8	#7 AND #4 Limits: Humans
#9	Lamivudine OR Zeffix OR Epivir OR 3TC
#10	Adefovir OR Hepsera OR Preveon
#11	#9 OR #10
#12	#7 AND #11 Limits: Publication date from 01/07/04, Humans
#13	#8 OR #12
	Total number of hits = 1057

Response appendix B: Revised flow diagram showing study identification for the systematic review



* The GLOBE study was included as two trials: one on HBeAg-positive patients and one on HBeAg-negative patients.

Response appendix C: Bibliographic list of non-RCT studies included in the systematic review

Lamivudine non-randomised trials	
1	Eun J, Lee HC, Lee SD, et al. The effect of lamivudine and adefovir dipivoxil on preventing hepatocellular carcinoma in hepatitis B virus-related liver cirrhosis. Presented at the 58th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Bostson MA, November 2-6 2007 2007: Abstact No. 961
2	Moskovitz DN, Osiowy C, Giles E, Tomlinson G, Heathcote EJ. Response to long-term lamivudine treatment (up to 5 years) in patients with severe chronic hepatitis B, role of genotype and drug resistance. J Viral Hepat 2005; 12(4): 398-404.
3	Papatheodoridis GV, Dimou E, Dimakopoulos K, et al. Outcome of hepatitis B e antigen-negative chronic hepatitis B on long-term nucleos(t)ide analog therapy starting with lamivudine. Hepatology 2005; 42(1): 121-9.
4	Ooga H, Suzuki F, Tsubota A, et al. Efficacy of lamivudine treatment in Japanese patients with hepatitis B virus-related cirrhosis. J Gastroenterol 2004; 39(11): 1078-84.
5	Barbon V, Gaia S, Marzano A, Lagget M, Rizzetto M. Prompt relapse of viremia after lamivudine discontinuation in e-minus chronic hepatitis B patients completely responders during 5 years of therapy. J Hepatol 2004; 41(3): 500-1.
6	Shin JW, Park NH, Jung SW, et al. Clinical significance of hepatitis B e antigen level measurement during long-term lamivudine therapy in chronic hepatitis B patients with e antigen positive. World J Gastroenterol 2006; 12(41): 6693-8.
7	Jang JW, Bae SH, Choi JY, et al. Early virological response predicts outcome during extended lamivudine retreatment in patients with chronic hepatitis B who relapsed after initial HBeAg responses. J Gastroenterol Hepatol 2006; 21(2): 384-91.
8	Zoulim F, Poynard T, Degos F, et al. A prospective study of the evolution of lamivudine resistance mutations in patients with chronic hepatitis B treated with lamivudine. J Viral Hepat 2006; 13(4): 278-88.
9	Neff GW, O'Brien C B, Nery J, et al. Outcomes in liver transplant recipients with hepatitis B virus: resistance and recurrence patterns from a large transplant center over the last decade. Liver Transpl 2004; 10(11): 1372-8.
10	Kawaoka T, Suzuki F, Akuta N, et al. Efficacy of lamivudine therapy in elderly patients with chronic hepatitis B infection. J Gastroenterol 2007; 42(5): 395-401.
11	Manolakopoulos S, Bethanis S, Elefsiniotis J, et al. Lamivudine monotherapy in HBeAg-negative chronic hepatitis B: prediction of response-breakthrough and long-term clinical outcome. Aliment Pharmacol Ther 2006; 23(6): 787-95.
12	Yoon SK, Jang JW, Kim CW, et al. Long-term results of lamivudine monotherapy in Korean patients with HBeAg-positive chronic hepatitis B: response and relapse rates, and factors related to durability of HBeAg seroconversion. Intervirology 2005; 48(6): 341-9.
13	Di Marco V, Marzano A, Lampertico P, et al. Clinical outcome of HBeAg-negative chronic hepatitis B in relation to virological response to lamivudine. Hepatology 2004; 40(4): 883-91.
14	Puoti M, Cozzi-Lepri A, Ancarani F, et al. The management of hepatitis B virus/HIV-1 co-infected patients starting their first HAART regimen. Treating two infections for the price of one drug? Antivir Ther 2004; 9(5): 811-7.
15	Puoti M, Cozzi-Lepri A, Arici C, et al. Impact of lamivudine on the risk of liver-related death in 2,041 HBsAg- and HIV-positive individuals: results from an inter-cohort analysis. Antivir Ther 2006; 11(5): 567-74.
16	Piroth L, Sene D, Pol S, et al. Epidemiology, diagnosis and treatment of chronic hepatitis B in HIV-infected patients (EPIB 2005 STUDY). Aids 2007; 21(10): 1323-31.
17	Ide T, Kumashiro R, Kuwahara R, et al. Clinical course of patients with chronic hepatitis B with viral breakthrough during long-term lamivudine treatment. J Gastroenterol 2005; 40(6): 625-30.
18	Study NUCB2014. Multicentre, open lavel, compassionate use programme for patients treated with 100 mg lamivudine once daily for up to 5 years. Data on file.
19	Matthews GV, Bartholomeusz A, Locarnini S, et al. Characteristics of drug resistant HBV in an international collaborative study of HIV-HBV-infected individuals on extended lamivudine therapy. Aids 2006; 20(6): 863-70.
20	Lok AS, Lai CL, Leung N, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. Gastroenterology 2003; 125(6): 1714-22.
21	Lai CL, Dienstag J, Schiff E, et al. Prevalence and clinical correlates of YMDD variants during lamivudine therapy for patients with chronic hepatitis B. Clin Infect Dis 2003; 36(6): 687-96.
22	Gaia S, Marzano A, Smedile A, et al. Four years of treatment with lamivudine: clinical and virological evaluations in HBe antigen-negative chronic hepatitis B. Aliment Pharmacol Ther 2004; 20(3): 281-7.
23	Kobayashi M, Suzuki F, Akuta N, et al. Response to long-term lamivudine treatment in patients infected with hepatitis B virus genotypes A, B, and C. J Med Virol 2006; 78(10): 1276-83.

24	Furusyo N, Takeoka H, Toyoda K, et al. Long-term lamivudine treatment for chronic hepatitis B in Japanese patients: a project of Kyushu University Liver Disease Study. World J Gastroenterol 2006; 12(4): 561-7.
25	Alexander G, Baba CS, Chetri K, Negi TS, Choudhuri G. High rates of early HBeAg seroconversion and relapse in Indian patients of chronic hepatitis B treated with Lamivudine: results of an open labeled trial. BMC Gastroenterol 2005; 5: 29.
26	Study NUCAB3017. A study of extended lamivudine treatment for hepatitis B subjects previously enrolled in phase II or phase III lamivudine trials. Data on file.
27	Kobayashi M, Suzuki F, Akuta N, et al. Loss of hepatitis B surface antigen from the serum of patients with chronic hepatitis treated with lamivudine. J Med Virol 2007; 79(10): 1472-7.
28	Arase Y, Ikeda K, Suzuki F, et al. Comparison of interferon and lamivudine treatment in Japanese patients with HBeAg positive chronic hepatitis B. J Med Virol 2007; 79(9): 1286-92.
29	Sun J, Wang Z, Ma S, et al. Clinical and virological characteristics of lamivudine resistance in chronic hepatitis B patients: a single center experience. J Med Virol 2005; 75(3): 391-8.
Tenofovir non-randomised trials	
30	van Bommel F, de Man R, Erhardt A, et al. First multicenter evaluation of the efficacy of tenofovir in nucleos(t)ide analog experienced patients with HBV monoinfection. Presented at the 58th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), 2007: Abstract No. 83 van Bommel F, de Man R, Erhardt A, et al. First multicenter evaluation of the efficacy of tenofovir in nucleos(t)ide analog experienced patients with HBV monoinfection. Hepatology 2007: 270A.
31	van Bommel F, Mauss S, Wunsche T, et al. No evidence for tenofovir resistance in patients with lamivudine-resistant HBV infection during long-term treatment for up to 5 years. American Association for the Study of Liver Diseases 2006.
32	Im GY, Uriel AJ, Carriero D, et al. Comparison of tenofovir versus adefovir based combination therapy in subjects with chronic hepatitis B. Hepatology 2005; 42(4 (Suppl 1)): 589A (abstract 999).
33	Hann HW, Chae HB, Dunn S. Tenofovir (TDF) has stronger antiviral effect than adefovir dipivoxil (ADV) against lamivudine (LAM) resistant hepatitis B virus (HBV). Digestive Disease Week 2006 2006: T-1841.
34	van Bommel F, Wunsche T, Mauss S, et al. Comparison of adefovir and tenofovir in the treatment of lamivudine-resistant hepatitis B virus infection. Hepatology 2004; 40(6): 1421-5.
35	van Bommel F, Feucht HH, Moller B, Spengler U, Sarrazin C, Huppe D, et al. Tenofovir rescue for patients with lamivudine resistant HBV infection with suboptimal virologic response to adefovir. Hepatology. 2005;42(4 (suppl 1)):589A (abstract 1000). van Bommel F, Zollner B, Sarrazin C, Spengler U, Huppe D, Moller B, et al. Tenofovir for patients with lamivudine-resistant hepatitis B virus (HBV) infection and high HBV DNA level during adefovir therapy. Hepatology. 2006 Aug;44(2):318-25.
Adefovir non-randomised trials	
36	Westland CE, Yang H, Delaney WEt, et al. Activity of adefovir dipivoxil against all patterns of lamivudine-resistant hepatitis B viruses in patients. J Viral Hepat 2005; 12(1): 67-73.
37	Izzedine H, Hulot JS, Launay-Vacher V, et al. Renal safety of adefovir dipivoxil in patients with chronic hepatitis B: two double-blind, randomized, placebo-controlled studies. Kidney Int 2004; 66(3): 1153-8.
38	Lampertico P, Viganò M, Iavarone M, et al. Low rates of genotypic resistance to adefovir in lamivudine resistant patients treated with adefovir-lamivudine combination therapy for 3 years. Podium presentation at the 41st Annual Meeting of the European Association for the Study of the Liver 2006 2006; Abstract No. 989. Lampertico P, Vigano M, Manenti E, et al. Low resistance to adefovir combined with Lamivudine: a 3-year study of 145 Lamivudine-resistant hepatitis B patients. Gastroenterology 2007; 133(5): 1445-51.
39	Lampertico P, Vigano M, Manenti E, et al. Adefovir rapidly suppresses hepatitis B in HBeAg-negative patients developing genotypic resistance to lamivudine. Hepatology 2005; 42(6): 1414-9.
40	Lampertico P, Viganò M, Manenti E, et al. Five years of sequential LAM to LAM+ADV therapy suppresses HBV replication in most HBeAg-negative cirrhotics, preventing decompensation but not hepatocellular carcinoma. Podium presentation at the 41st Annual Meeting of the European Association for the Study of the Liver. Presentation No. 85 2006.
41	Buti M, Elefsiniotis I, Jardi R, et al. Viral genotype and baseline load predict the response to adefovir treatment in lamivudine-resistant chronic hepatitis B patients. J Hepatol 2007; 47(3): 366-72.
42	Borroto-Esoda K, Miller MD, Arterburn S. Pooled analysis of amino acid changes in the HBV polymerase in patients from four major adefovir dipivoxil clinical trials. J Hepatol 2007; 47(4): 492-8.
43	Lampertico P, Marzano A, Levrero M, et al. A multicenter Italian study of rescue adefovir dipivoxil therapy in lamivudine resistant patients: a 2-year analysis of 604 patients. Hepatology 2005; 42(4 (Suppl 1)): 591A.
44	Schiff E, Lai CL, Hadziyannis S, et al. Adefovir dipivoxil for the treatment of CHB in pre-liver transplantation

	patients with lamivudine-resistant HBV. Oral presentation at AASLD Annual meeting 2003, October 26, Boston, Massachusetts, USA 2003. Schiff E, Lai CL, Neuhaus P, et al. Long term safety and efficacy of Adefovir Dipivoxil (ADV) in the treatment of chronic hepatitis B in patients pre and post liver transplant (OLT) with lamivudine resistant (LAM-R) hepatitis B virus (HBV). Poster presentation at the 55th Annual Meeting of the American Association for the Study of Liver Diseases, October 29-November 2, Boston Massachusetts USA (Poster No 1143) 2004
Entecavir non-randomised studies	
45	Colonno RJ, Rose R, Baldick CJ, et al. Entecavir resistance is rare in nucleoside naive patients with hepatitis B. Hepatology 2006; 44(6): 1656-65.
46	Colonno RJ, Rose RE, Pokornowski K, et al. Four Year Assessment of Entecavir Resistance in Nucleoside Naïve and Lamivudine Refractory Patients. Podium presentation at the 42nd Annual Meeting of the European Association for the Study of the Liver, Barcelona, Spain 2007

Response appendix D: Full bibliographical details and reasons for excluding the 29 trials that did not meet the criteria for the MTC

	Study	Reason for exclusion
1	Marcellin P, Lau GK, Bonino F, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2004; 351(12): 1206-17. Marcellin P, Lau GKK, Bonino F, et al. Peginterferon alfa-2A (40KD) (PEGASYS®) monotherapy is more effective than lamivudine monotherapy in the treatment of HBeAg-negative chronic hepatitis B: 72-week results from a phase III, partially double-blind study of PEGASYS® alone vs PEGASYS® plus lamivudine vs lamivudine [EASL abstract]. Journal of Hepatology 2004; 40(Suppl 1): 34. Bonino F, Marcellin P, Lau GK, et al. Predicting response to peginterferon alpha-2a, lamivudine and the two combined for HBeAg-negative chronic hepatitis B. Gut 2007; 56(5): 699-705.	C
2	Yao G, Wang B, Cui Z, Yao J, Zeng M. A randomized double-blind placebo-controlled study of lamivudine in the treatment of patients with chronic hepatitis B virus infection. Chin Med J (Engl) 1999; 112(5): 387-91. Yao GB, Cui ZY, Wang BE, Yao JL, Zeng MD. A 3-year clinical trial of lamivudine in treatment of patients with chronic hepatitis B. Hepatobiliary Pancreat Dis Int 2004; 3(2): 188-93.	B
3	Yalcin K, Degertekin H, Yildiz F, Celik Y. Comparison of 12-month courses of interferon-alpha-2b-lamivudine combination therapy and interferon-alpha-2b monotherapy among patients with untreated chronic hepatitis B. Clin Infect Dis 2003; 36(12): 1516-22.	C
4	Tassopoulos NC, Volpes R, Pastore G, et al. Efficacy of lamivudine in patients with hepatitis B e antigen-negative/hepatitis B virus DNA-positive (precore mutant) chronic hepatitis B.Lamivudine Precore Mutant Study Group. Hepatology 1999; 29(3): 889-96. Rizzetto M, Tassopoulos NC, Goldin RD, et al. Extended lamivudine treatment in patients with HBeAg-negative chronic hepatitis B. J Hepatol 2005; 42(2): 173-9.	B
5	Yalcin K, Yildiz F, Degertekin H, Celik Y. A 12 month course of interferon and lamivudine combination therapy versus interferon monotherapy for untreated chronic hepatitis B infection. Journal of Hepatology 2002; 36(Suppl 1): 138.	C
6	Naoumov NV, Lopes AR, Burra P, et al. Randomized trial of lamivudine versus hepatitis B immunoglobulin for long-term prophylaxis of hepatitis B recurrence after liver transplantation. J Hepatol 2001; 34(6): 888-94.	C
7	Schalm SW, Heathcote J, Cianciara J, et al. Lamivudine and alpha interferon combination treatment of patients with chronic hepatitis B infection: a randomised trial. Gut 2000; 46(4): 562-8.	C
8	Dore GJ, Cooper DA, Barrett C, et al. Dual efficacy of lamivudine treatment in human immunodeficiency virus/hepatitis B virus-coinfected persons in a randomized, controlled study (CAESAR). The CAESAR Coordinating Committee. J Infect Dis 1999; 180(3): 607-13.	A
9	van Zonneveld M, Zobdervan P, Man.R.A. d, Schalm SW, Janssen HLA. Liver histology in chronic hepatitis B patients after 1 year of treatment with pegylated interferon alpha-2b in combination with lamivudine or placebo. Journal of Hepatology 2004; 40(S1): 132.	C
10	Kaymakoglu S, Demir K, Cakaloglu Y, et al. Lamivudine and alpha interferon combination therapy in patients with anti-HBE-positive chronic hepatitis B: preliminary results of a randomised study. Journal of Hepatology 2001; 34(Supplement 1): 171.	C
11	Saruc M, Ozden N, Turkel N, et al. Long term efficacy of interferon and thymosin combination in comparison to lamivudine+interferon and interferon monotherapy in patients with HBEAG negative chronic hepatitis B. Journal of Hepatology 2003; 38(Supplement 2): 169.	C
12	Lee KW, Lee SK, Joh JW, et al. Comparison of the efficacy in prevention of hepatitis B virus recurrence after liver transplantation between HBIG and lamivudine. Transplant Proc 2001; 33(7-8): 3643-4.	A
13	Lai CL, Ching CK, Tung AK, et al. Lamivudine is effective in suppressing hepatitis B virus DNA in Chinese hepatitis B surface antigen carriers: a placebo-controlled trial. Hepatology	

	1997; 25(1): 241-4.	
14	Kim YJ, Kim BG, Jung JO, Yoon JH, Lee HS. High rates of progressive hepatic functional deterioration whether lamivudine therapy is continued or discontinued after emergence of a lamivudine-resistant mutant: a prospective randomized controlled study. J Gastroenterol 2006; 41(3): 240-9.	B
15	Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004; 351(15): 1521-31.	B
16	Yalçin K, De, ertekin H, et al. A three-month course of lamivudine therapy in HBeAg-positive hepatitis B patients with normal aminotransferase levels. The Turkish journal of gastroenterology : the official journal of Turkish Society of Gastroenterology 2004; 15(1): 14-20.	B
17	Jang JW, Choi JY, Bae SH, et al. A randomized controlled study of preemptive lamivudine in patients receiving transarterial chemo-lipiodolization. Hepatology 2006; 43(2): 233-40.	A
18	Chan HL, Wang H, Niu J, Chim AM, Sung JJ. Two-year lamivudine treatment for hepatitis B e antigen-negative chronic hepatitis B: a double-blind, placebo-controlled trial. Antivir Ther 2007; 12(3): 345-53.	B
19	Xu WM, Cui YT, Wang L, et al. Efficacy and safety of lamivudine in late pregnancy for the prevention of mother-child transmission of hepatitis B; a multicentre, randomised, double-blind, placebo-controlled study. Hepatology 2004; 40(4 Supl 1): 272a-3a.	A
20	Jang JW, Choi JY, Kim CW, et al. Theraputic role of preempive lamivudine therapy for the prevention of hepatitis B virus reactivation in patients with hepatocellular carcinoma undergoing transarterial chemolipiodolization: a randomized controlled study. Hepatology 2005; 42(4 Suppl 1): 594a.	A
21	Lau G, PiratvisuthT, Luo KX, et al. Peginterferon alfa-2A (40KD) (PEGASYS) monotherapy and in combination with lamivudine is more effective than lamivudine monotherapy in HBeAg-positive chronic hepatitis B: results from a large, multinational study. Hepatology 2004; 40(4 Suppl 1): 171a. Lau GK, Piratvisuth T, Luo KX, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. N Engl J Med 2005; 352(26): 2682-95.	C
22	Lau GKK, Luo KX, Paik SW, et al. Effect of age, gender, prior anti-HBV therapy and drug exposure on sustained response in Asian patients enrolled in a large multinational study of peginterferon alfa-2a (40 kDA) + lamivudine vs lamivudine for chronic hepatitis B. Liver International 2005; 25(6): 1296. Piratvisuth T, Lau GKK, Chao YC, et al. Sustained response in Asian patients enrolled in two large, multinational studies of peginterferon alfa-2a (40 kDa) + lamivudine vs lamivudine for chronic hepatitis B. Liver International 2005; 25(6): 1296.	C
23	Janssen HL, van Zonneveld M, Senturk H, et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. Lancet 2005; 365(9454): 123-9.	C
24	Niro GA, Lagget M, Tillman HL, et al. Efficacy of lamivudine therapy in chronic delta hepatitis: a mulicenter randomised controlled pilot study. J Hepatol 2003; 38 (suppl 2): 159 (abstract 548).	
25	Study ZEFT01. A double blind randomised multicentre study of lamivudine added to the current treatment in the therapy of chronic hepatitis B in HBV-DNA/anti-HBe positive subjects. Data on file 2005.	C
26	Study ZEFT02. Open-label study of lamivudine in combination with interferon in treating chronic hepatitis B, anti HBe positive patients who are interferon-therapy naive. Data on file 2007.	C
27	Study ZEFT03. Open label treatment with lamivudine in patients with chronic hepatitis B, anti HBe (hepatitis B envelope) positive, who have not responded to previous treatment with interferon. Study of lamivudine added to the interferon treatment in comparison to the sequential treatment. Data on file 2005.	C
28	Study NUC40021. A stratified, partially randomised (stratum B only), double blind, multicentre trial of lamivudine and adefovir dipivoxil treatment for patients with chronic hepatitis B who have shown disease progression by reaching a clinical endpoint. Data on file 2005.	B
29	Piratvisuth T, Marcellin P, Lau G, et al. ALT flares and sustained alt response in patients with HBeAg-negative chronic hepatitis B treated with peginterferon alfa-2a (40KD) (PEGASYS), peginterferon alfa-2A (40KD) plus lamivudine or lamivudine alone. Hepatology	C

	2004; 40(4 Suppl 1): 656a-7a.	
30	Study NUC30935. A randomised, multicenter, placebo-controlled study to assess the efficacy and optimal duration of lamivudine treatment in patients with pre-core mutant HBV. Data on file 2006.	B
31	Study NUCB2002. A randomized, multicentre, single-blind (patient), placebo-controlled, phase II, dose-ranging study to determine the pharmacokinetics, safety, and preliminary activity of once-daily lamivudine in patients with chronic hepatitis B infection. Data on file 2005.	B
32	Study LB-02. Phase III study of lamivudine – a placebo-controlled, double-blind study of lamivudine in chronic hepatitis B – (protocol no: LB-02). 2005.	B
33	Study NUC30907. A randomized, double-blind, placebo-controlled study of the treatment of HBsAg positive subjects after stable renal transplantation with lamivudine. Data on file 2005.	A
34	Study NUCB3026. A double-blind, placebo-controlled study of lamivudine in subjects in China with chronic hepatitis B infection followed by long-term (5 years) lamivudine treatment. Data on file 2005.	B
35	GJ, Cooper DA, Pozniak AL, et al. Efficacy of tenofovir disoproxil fumarate in antiretroviral therapy-naive and -experienced patients coinfected with HIV-1 and hepatitis B virus. J Infect Dis 2004; 189(7): 1185-92.	A
36	Dore G, Cooper D, Pozniak AL, et al. Anti-hepatitis B virus (HBV) activity in HBV/HIV co-infected patients treated with tenofovir DF (TDF) and lamivudine (LAM) versus LAM alone: 144-week follow-up. 15th International AIDS conference 2004: Abstract 3308.	A
37	Peters MG, Andersen J, Lynch P, et al. Randomized controlled study of tenofovir and adefovir in chronic hepatitis B virus and HIV infection: ACTG A5127. Hepatology 2006; 44(5): 1110-6.	D
38	Gilead Sciences. Study GS-US-174-0106: A phase 2, randomized, double-blind study exploring the efficacy, safety and tolerability of tenofovir disoproxil fumarate (DF) monotherapy versus emtricitabine plus tenofovir DF fixed-dose combination therapy in subjects currently being treated with adefovir dipivoxil for chronic hepatitis B and having persistent viral replication. Data on file 2007.	B
39	Gilead Sciences. Study GS-US-174-0108: A phase 2, double-blind, multi-center, randomized study comparing tenofovir disoproxil fumarate, emtricitabine plus tenofovir disoproxil fumarate, and entecavir in the treatment of chronic hepatitis B subjects with decompensated liver disease and in the prevention of hepatitis B recurrence post-transplantation. Data on file 2007.	B
40	Marcellin P, Chang TT, Lim SG, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. N Engl J Med 2003; 348(9): 808-16. Marcellin P, Chang TT, Lim S, et al. Long term efficacy and safety of adefovir dipivoxil (ADV) 10 MG in HBeAg+ chronic hepatitis B (CHB) patients: increasing serologic, virologic and biochemical response over time. Hepatology 2004; 40(4 Suppl 1): 655a. Marcellin P, Chang T, Lim S, et al. Increasing serologic, virologic and biochemical response over time to adefovir dipivoxil (ADV) 10 mg in HBeAg+ chronic hepatitis B (CHB) patients. Journal of Hepatology 2005; 42(Suppl 2): 31-2. Durantel S, Werle B, Durantel D, et al. Different profiles of response to adefovir dipivoxil and factors that may influence response in patients with chronic hepatitis B. Hepatology 2004; 40(4 Suppl 1): 654a. Marcellin P, Chang TT, Lim SG, et al. Long-term efficacy and safety of adefovir dipivoxil for the treatment of HBeAg-positive chronic hepatitis B (CHB) patients in study GS-98-437. 57th Annual Meeting of the American Association for the Study of Liver Diseases, Boston, Massachusetts, USA 2006; October 27–31: Poster 969. Werle B, Cinquin K, Marcellin P, et al. Evolution of hepatitis B viral load and viral genome sequence during adefovir dipivoxil therapy. Journal of viral hepatitis 2004; 11(1): 74-83.	B
41	Koskinas J, Manesis EK, Kountouras D, et al. Adefovir dipivoxil alone or in combination with lamivudine in HBeAg negative patients with lamivudine resistant chronic hepatitis B: a prospective, randomized study. Journal of Hepatology 2005; 42(Suppl 2): 181.	B
42	Heathcote EJ, Jeffers L, Wright T, Sherman M, Perrillo R, Sacks S, et al. The loss of serum HBV DNA and HBeAg and seroconversion following short-term (12 weeks) adefovir	B

	dipivoxil therapy in chronic hepatitis B: two placebo-controlled Phase II studies. Hepatology.1998;28(Suppl 4 Pt 2):317 A.	
43	Zeng MD, Yao GB, Wang YZ, et al. One year results from a multi-centre, double-blind, placebo (PLA)-controlled 5 year study of adefovir dipivoxil (ADV) in Chinese patients with HBeAg positive chronic hepatitis B (CHB). Hepatology 2004; 40(4 Suppl 1): 730a. Zeng M, Mao Y, Yao G, et al. A double-blind randomized trial of adefovir dipivoxil in Chinese subjects with HBeAg-positive chronic hepatitis B. Hepatology 2006; 44(1): 108-16. Mao Y, Zeng M, Gao Z, et al. Efficacy, safety and low resistance of three years therapy with adefovir dipivoxil (ADV) in Chinese patients with HBEAG positive chronic hepatitis B (CHB). Hepatology 2006; 44(4 (Suppl 1)): 699a.	B
44	Ghany M, Lutchman G, Kleiner D, et al. Lamivudine and adefovir versus adefovir alone for HBeAg-positive chronic hepatitis B. Hepatology 2005; 42(4 Suppl 1): 591a-2a.	D
45	Tziomalos K, Vassiliadis T, Giouleme O, et al. Adefovir dipivoxil plus lamivudine combination treatment is superior to adefovir dipivoxil monotherapy in lamivudine-resistant hepatitis B e antigen-negative chronic hepatitis B patients. Presented at the 58th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Bostson MA, November 2-6 2007 2007: Abstract No 956.	B
46	Borroto-Esoda K, MIller MD, Reiser H. Clinical virology report review and approval: adefovir dipivoxil integrated resistance summary. Fourth Edition: May 18, 2006. 2006. Gilead Sciences. Final clinical study report for adefovir dipivoxil study GS-98-438: A Phase III double-blind, randomized, placebo-controlled study of adefovir dipivoxil for the treatment of patients with presumed precore mutant (HBeAg-/Anti-HBe /HBV DNA) chronic hepatitis B virus infection with open label long term follow-up (3 additional years) of safety, efficacy, and resistance of adefovir dipivoxil for the treatment of patients with presumed precore mutant chronic hepatitis B virus infection. 2005.	D
47	de Man RA, Wolters LM, Nevens F, et al. Safety and efficacy of oral entecavir given for 28 days in patients with chronic hepatitis B virus infection. Hepatology 2001; 34(3): 578-82.	B
48	Yao G, Zhou X, Xu D, et al. A randomized, placebo-controlled study (ETV-056) in China of the efficacy and safety of entecavir in chronic hepatitis B patients who have failed lamivudine. Hepatology 2004; 40(4 Suppl 1): 674a.	B
49	Lai C, Rosmawati M, Lao J, et al. A phase II study of Entecavir vs Lamivudine in adults with chronic hepatitis B [abstract]. Journal of Hepatology 2001; 34(1): 24.	B
50	Yao GB, Xu D, Wang B, et al. A phase II study in China of the safety and antiviral activity of entecavir in adults with chronic hepatitis B infection [AASLD abstract]. Hepatology 2003; 38(4 Suppl 1): 711a.	B
51	Lai CL, Rosmawati M, Lao J, et al. Entecavir is superior to lamivudine in reducing hepatitis B virus DNA in patients with chronic hepatitis B infection. Gastroenterology 2002; 123(6): 1831-8.	B
52	Sollano J, Schiff E, Carrilho F, et al. Entecavir is well-tolerated for treatment of chronic hepatitis B: phase III safety analysis in nucleoside-naive and lamivudine-refractory patients. Hepatology 2004; 40(4 Suppl 1): 665a.	B
53	Wong DK, Yuen MF, Ngai VW, Fung J, Lai CL. One-year entecavir or lamivudine therapy results in reduction of hepatitis B virus intrahepatic covalently closed circular DNA levels. Antivir Ther 2006; 11(7): 909-16.	B
54	Tenney DJ, Rose RE, Baldick CJ, et al. Two-year assessment of entecavir resistance in Lamivudine-refractory hepatitis B virus patients reveals different clinical outcomes depending on the resistance substitutions present. Antimicrob Agents Chemother 2007; 51(3): 902-11	B

Exclusion codes:

A	Patient population	Patients were exclusively; pregnant women; pre-, post- or peri-transplant; with decompensated cirrhosis, cancer or inactive liver disease
B	Reported outcomes	Study did not report one of the following outcomes after 40-72 weeks of therapy;

- Percentage/number of patients with HBV DNA levels below a threshold of 1,000 copies/ml
- Percentage/number of patients with HBeAg seroconversion or loss

C Study arms — Study arms evaluating interferons, unlicensed treatments/doses or sequential use of several treatments within the same 12 month period

Following exclusion of any arms using interferons or unlicensed therapies study had fewer than 2 treatment arms

D Patient population — Entire trials (or a patient subgroup for which sufficient results were reported) did not meet criteria for one of the following analyses

	Treatment-naïve HBeAg +ve	**Treatment-naïve HBeAg –ve**	**LAM-R HBeAg +ve**	**LAM-R HBeAg –ve**	**Treatment-naïve HBeAg +ve/-ve combined**
Permitted % pts HBeAg +ve at baseline	>66.7%	<33.3%	>66.7%	<33.3%	Any
Permitted % pts LAM refractory* at baseline	<33.3%	<33.3%	≥66.7%	≥66.7%	<33.3%
Permitted % pts HIV co-infected	<50%	<50%	<50%	<50%	<50%

Response appendix E:

Ref 1. Estimated population, births, stillbirths, deaths and marriages, numbers and rates, by administrative area, Scotland, 2006 [1]

	Estimated population at 30 June 2005	Deaths							
Area	Both sexes	Males	Females	Both sexes		Males		Females	
				Number	Rate [2]				
SCOTLAND	**5,094,800**	**2,456,109**	**2,638,691**	**55,089**	**11**	**26,260**	1.07%	**28,829**	1.09%

http://www.gro-scotland.gov.uk/files1/stats/06pr-p1.xls

[1] All data are provisional except populations which refer to 2005.

[2] Rate per 1,000 population (based on 2005 mid-year population estimates)

Table 1: Disaggregated base case results for HBeAg-positive patients using alternative mortality rates suggested by the ERG. Unless otherwise specified, all costs and benefits are discounted at 3.5% per annum.

Treatment strategy	Drug cost Rx1 (Disc)	Other drug cost (Disc)	Disease management cost (Disc)	Total cost/pt		Life years/pt	Total QALYs/ pt	
				Disc	Undisc		Disc	Undisc
BSC	£0	£0	£8,243	£8,243	£11,917	20.21	13.56	16.36
LAM then BSC	£2,910	£0	£8,528	£11,438	£15,570	20.83	14.05	16.96
LAM then TDF	£2,910	£6,822	£8,624	£18,356	£27,811	22.43	15.08	18.33
LAM then ADV	£2,910	£7,733	£8,780	£19,423	£28,562	21.80	14.68	17.79
LAM then ETV	£2,910	£10,188	£9,080	£22,178	£30,092	20.88	13.99	16.89
LAM then TDF+LAM	£2,910	£10,012	£8,762	£21,684	£34,101	22.61	15.18	18.47
TDF then BSC	£15,007	£0	£9,896	£24,903	£36,101	23.18	15.61	19.02
TDF then LAM	£15,007	£25	£9,899	£24,930	£36,154	23.20	15.62	19.03
TDF then ETV	£15,007	£197	£9,908	£25,112	£36,466	23.19	15.62	19.02
TDF then TDF+LAM	£15,007	£246	£9,917	£25,170	£36,680	23.23	15.64	19.05
TDF then TDF+LAM then ETV	£15,007	£247	£9,917	£25,171	£36,683	23.23	15.64	19.05
ADV then LAM	£17,154	£260	£10,605	£28,019	£38,456	22.36	15.06	18.29
LAM then ADV+LAM	£2,910	£14,704	£9,472	£27,086	£41,690	22.02	14.72	17.86
ADV then TDF	£17,154	£1,732	£10,794	£29,680	£41,993	22.63	15.21	18.49
ADV then TDF+LAM	£17,154	£2,558	£10,843	£30,555	£43,910	22.68	15.24	18.53
ADV then ADV+LAM	£17,154	£3,367	£10,931	£31,452	£45,390	22.56	15.14	18.41
ETV then LAM	£22,307	£76	£11,082	£33,465	£47,436	23.03	15.50	18.87
ADV+LAM then TDF+LAM	£20,043	£2,029	£11,782	£33,854	£48,543	22.57	15.21	18.48
ETV then TDF	£22,307	£509	£11,134	£33,950	£48,502	23.11	15.54	18.93
ETV+ADV then LAM	£41,587	£31	£14,232	£55,850	£78,952	23.10	15.54	18.92

Table 2: Disaggregated base case results for HBeAg-negative patients using alternative mortality rates suggested by the ERG. Unless otherwise specified, all costs and benefits are discounted at 3.5% per annum.

Treatment strategy	Drug cost Rx1 (Disc)	Other drug cost (Disc)	Disease management cost (Disc)	Total cost/pt		Life years/pt	Total QALYs/ pt	
				Disc	Undisc		Disc	Undisc
BSC	£0	£0	£12,442	£12,442	£18,075	15.25	9.89	11.50
LAM then BSC	£4,109	£0	£12,834	£16,944	£23,272	15.59	10.11	11.75
LAM then TDF	£4,109	£20,350	£15,277	£39,736	£61,606	19.23	12.09	14.39
LAM then ADV	£4,109	£19,884	£15,038	£39,032	£57,346	17.21	10.94	12.84
LAM then ETV	£4,109	£15,951	£13,510	£33,570	£45,499	16.67	10.73	12.55
LAM then TDF+LAM	£4,109	£31,350	£15,997	£51,457	£82,950	20.05	12.50	14.97
TDF then BSC	£36,542	£0	£14,530	£51,072	£77,982	21.20	13.30	16.00
TDF then LAM	£36,542	£81	£14,555	£51,178	£78,179	21.23	13.32	16.02
TDF then ETV	£36,542	£549	£14,572	£51,663	£79,019	21.25	13.33	16.03
TDF then TDF+LAM	£36,542	£1,021	£14,657	£52,220	£80,347	21.36	13.38	16.11
TDF then TDF+LAM then ETV	£36,542	£1,024	£14,657	£52,224	£80,356	21.36	13.38	16.11
ADV then LAM	£34,467	£791	£14,702	£49,960	£70,470	18.58	11.78	13.95
LAM then ADV+LAM	£4,109	£34,672	£16,409	£55,190	£87,721	18.92	11.83	14.04
ADV then TDF	£34,467	£6,654	£15,620	£56,742	£84,007	19.68	12.34	14.72
ADV then TDF+LAM	£34,467	£10,156	£15,877	£60,501	£91,731	19.95	12.47	14.90
ADV then ADV+LAM	£34,467	£11,253	£15,969	£61,689	£93,581	19.58	12.26	14.61
ETV then LAM	£51,196	£243	£14,571	£66,009	£98,058	20.72	13.03	15.62
ADV+LAM then TDF+LAM	£45,453	£7,879	£16,289	£69,622	£103,541	19.51	12.19	14.52
ETV then TDF	£51,196	£2,000	£14,824	£68,019	£102,281	21.05	13.19	15.86
ETV+ADV then LAM	£97,363	£104	£15,059	£112,527	£166,769	21.01	13.17	15.83

Table 3: Disaggregated base case results for HBeAg-positive patients with amended transition between HBeAg seroconverted state to compensated cirrhosis state as discussed in B5b. Unless otherwise specified, all costs and benefits are discounted at 3.5% per annum.

Treatment strategy	Drug cost Rx1 (Disc)	Other drug cost (Disc)	Disease management cost (Disc)	Total cost/pt		Life years/pt	Total QALYs/ pt	
				Disc	Undisc		Disc	Undisc
BSC	£0	£0	£9,995	£9,995	£15,249	24.76	16.33	20.02
LAM then BSC	£3,139	£0	£10,426	£13,565	£19,511	25.53	16.90	20.75
LAM then TDF	£3,139	£9,082	£10,913	£23,134	£37,548	27.95	18.39	22.75
LAM then ADV	£3,139	£9,910	£10,973	£24,023	£37,527	26.95	17.78	21.92
LAM then ETV	£3,139	£11,913	£11,112	£26,164	£37,144	25.70	16.90	20.75
LAM then TDF+LAM	£3,139	£13,510	£11,137	£27,786	£46,890	28.26	18.56	22.98
TDF then BSC	£18,477	£0	£12,440	£30,917	£48,360	29.11	19.15	23.75
TDF then LAM	£18,477	£34	£12,446	£30,958	£48,444	29.12	19.16	23.77
TDF then ETV	£18,477	£262	£12,459	£31,199	£48,885	29.12	19.16	23.76
TDF then TDF+LAM	£18,477	£365	£12,479	£31,321	£49,284	29.17	19.19	23.80
TDF then TDF+LAM then ETV	£18,477	£366	£12,479	£31,322	£49,287	29.17	19.19	23.80
ADV then LAM	£20,216	£348	£13,030	£33,594	£49,129	27.78	18.32	22.63
LAM then ADV+LAM	£3,139	£18,897	£11,880	£33,916	£55,574	27.37	17.91	22.11
ADV then TDF	£20,216	£2,505	£13,344	£36,064	£54,646	28.23	18.56	22.97
ADV then TDF+LAM	£20,216	£3,733	£13,421	£37,371	£57,644	28.32	18.60	23.03
ADV then ADV+LAM	£20,216	£4,745	£13,521	£38,482	£59,525	28.11	18.47	22.84
ETV then LAM	£27,141	£104	£13,689	£40,935	£62,354	28.85	18.97	23.52
ADV+LAM then TDF+LAM	£24,051	£2,932	£14,440	£41,424	£63,672	28.12	18.52	22.91
ETV then TDF	£27,141	£750	£13,778	£41,670	£64,053	28.98	19.05	23.62
ETV+ADV then LAM	£50,914	£43	£17,126	£68,083	£103,434	28.97	19.04	23.61

Table 4: Disaggregated base case results for HBeAg-negative patients with amended transition between HBeAg seroconverted state to compensated cirrhosis state as discussed in B5b. Unless otherwise specified, all costs and benefits are discounted at 3.5% per annum.

Treatment strategy	1st line drug cost	2nd/3rd linedrug cost	Disease management cost	Total cost/pt		Life years/pt (Undisc)	Total QALYs/ pt	
				Disc	Undisc		Disc	Undisc
BSC	£0	£0	£14,331	£14,331	£21,573	18.39	11.75	13.90
LAM then BSC	£4,283	£0	£14,852	£19,135	£27,218	18.77	11.99	14.18
LAM then TDF	£4,283	£24,481	£18,073	£46,837	£75,643	23.78	14.70	17.84
LAM then ADV	£4,283	£23,294	£17,597	£45,173	£68,555	20.90	13.08	15.62
LAM then ETV	£4,283	£17,945	£15,750	£37,978	£52,853	20.18	12.80	15.23
LAM then TDF+LAM	£4,283	£38,287	£19,005	£61,575	£103,675	24.97	15.30	18.67
TDF then BSC	£42,557	£0	£17,390	£59,948	£96,041	26.59	16.39	20.10
TDF then LAM	£42,557	£99	£17,423	£60,079	£96,295	26.63	16.41	20.13
TDF then ETV	£42,557	£680	£17,446	£60,683	£97,387	26.66	16.42	20.15
TDF then TDF+LAM	£42,557	£1,340	£17,558	£61,455	£99,278	26.83	16.51	20.27
TDF then TDF+LAM then ETV	£42,557	£1,345	£17,558	£61,460	£99,291	26.83	16.51	20.27
ADV then LAM	£38,739	£942	£17,355	£57,037	£83,536	22.81	14.23	17.16
LAM then ADV+LAM	£4,283	£41,955	£19,406	£65,644	£108,567	23.31	14.33	17.33
ADV then TDF	£38,739	£8,494	£18,559	£65,792	£101,661	24.40	15.04	18.28
ADV then TDF+LAM	£38,739	£13,112	£18,892	£70,743	£112,246	24.79	15.23	18.55
ADV then ADV+LAM	£38,739	£14,419	£18,980	£72,138	£114,395	24.23	14.91	18.10
ETV then LAM	£59,224	£299	£17,411	£76,933	£119,660	25.88	15.99	19.55
ADV+LAM then TDF+LAM	£51,400	£10,145	£19,315	£80,860	£125,610	24.16	14.83	18.02
ETV then TDF	£59,224	£2,619	£17,746	£79,589	£125,450	26.36	16.23	19.89
ETV+ADV then LAM	£113,307	£128	£17,995	£131,431	£204,248	26.30	16.20	19.85

Amended Table 37: Disaggregated base case results for HBeAg-negative patients (based on deterministic base case). Unless otherwise specified, all costs and benefits are discounted at 3.5% per annum.

Treatment strategy	1st line drug cost	2nd/3rd linedrug cost	Disease management cost	Total cost/pt		Life years/pt (Undisc)	Total QALYs/ pt	
				Disc	Undisc		Disc	Undisc
BSC	£0	£0	£14,331	£14,331	£21,573	18.39	11.75	13.9
LAM then BSC	£4,283	£0	£14,852	£19,135	£27,218	18.77	11.99	14.18
LAM then TDF	£4,283	£24,481	£18,073	£46,837	£75,643	23.78	14.7	17.84
LAM then ADV	£4,283	£23,294	£17,597	£45,173	£68,555	20.9	13.08	15.62
LAM then ETV	£4,283	£17,945	£15,750	£37,978	£52,853	20.18	12.8	15.23
LAM then TDF+LAM	£4,283	£38,287	£19,005	£61,575	£103,675	24.97	15.3	18.67
TDF then BSC	£42,557	£0	£17,390	£59,948	£96,041	26.59	16.39	20.1
TDF then LAM	£42,557	£99	£17,423	£60,079	£96,295	26.63	16.41	20.13
TDF then ETV	£42,557	£680	£17,446	£60,683	£97,387	26.66	16.42	20.15
TDF then TDF+LAM	£42,557	£1,340	£17,558	£61,455	£99,278	26.83	16.51	20.27
TDF then TDF+LAM then ETV	£42,557	£1,345	£17,558	£61,460	£99,291	26.83	16.51	20.27
ADV then LAM	£38,739	£942	£17,355	£57,037	£83,536	22.81	14.23	17.16
LAM then ADV+LAM	£4,283	£41,955	£19,406	£65,644	£108,567	23.31	14.33	17.33
ADV then TDF	£38,739	£8,494	£18,559	£65,792	£101,661	24.4	15.04	18.28
ADV then TDF+LAM	£38,739	£13,112	£18,892	£70,743	£112,246	24.79	15.23	18.55
ADV then ADV+LAM	£38,739	£14,419	£18,980	£72,138	£114,395	24.23	14.91	18.1
ETV then LAM	£59,224	£299	£17,411	£76,933	£119,660	25.88	15.99	19.55
ADV+LAM then TDF+LAM	£51,400	£10,145	£19,315	£80,860	£125,610	24.16	14.83	18.02
ETV then TDF	£59,224	£2,619	£17,746	£79,589	£125,450	26.36	16.23	19.89
ETV+ADV then LAM	£113,307	£128	£17,995	£131,431	£204,248	26.3	16.2	19.85

Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

Response appendix F:

7.3.3. Sensitivity analysis

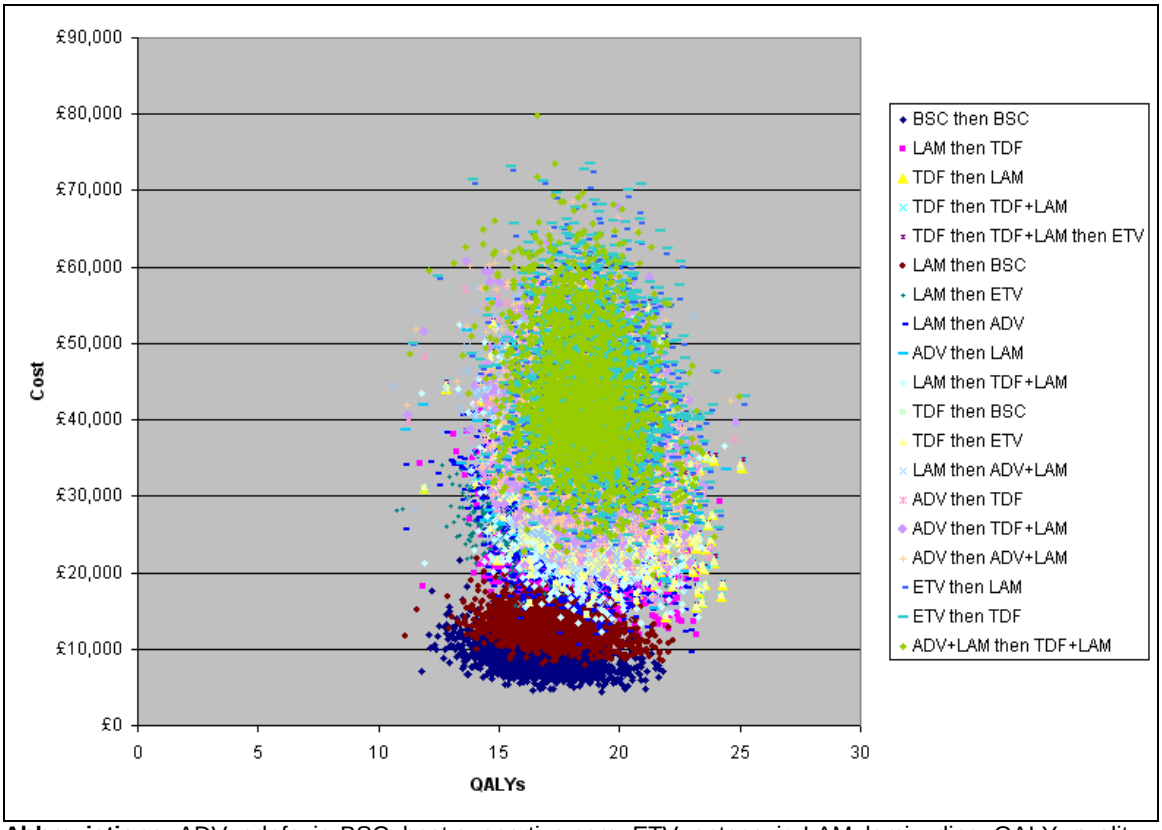
7.3.3.1. What were the main findings of the sensitivity analyses?

7.3.3.1.1. Probabilistic sensitivity analysis: HBeAg-positive patients

All parameters other than unit costs were varied simultaneously in probabilistic sensitivity analysis. All 20 strategies shown in Table 36 were subjected to PSA (Figure 9). It was not feasible to conduct PSA on all 211 treatment strategies listed in Appendix 11 due to the time taken to conduct the simulations; however, since the strategies included in PSA covered all of the main clusters lying on or near the frontier, restricting the number of strategies is unlikely to have any significant effect on the probability that first-line tenofovir is cost-effective.

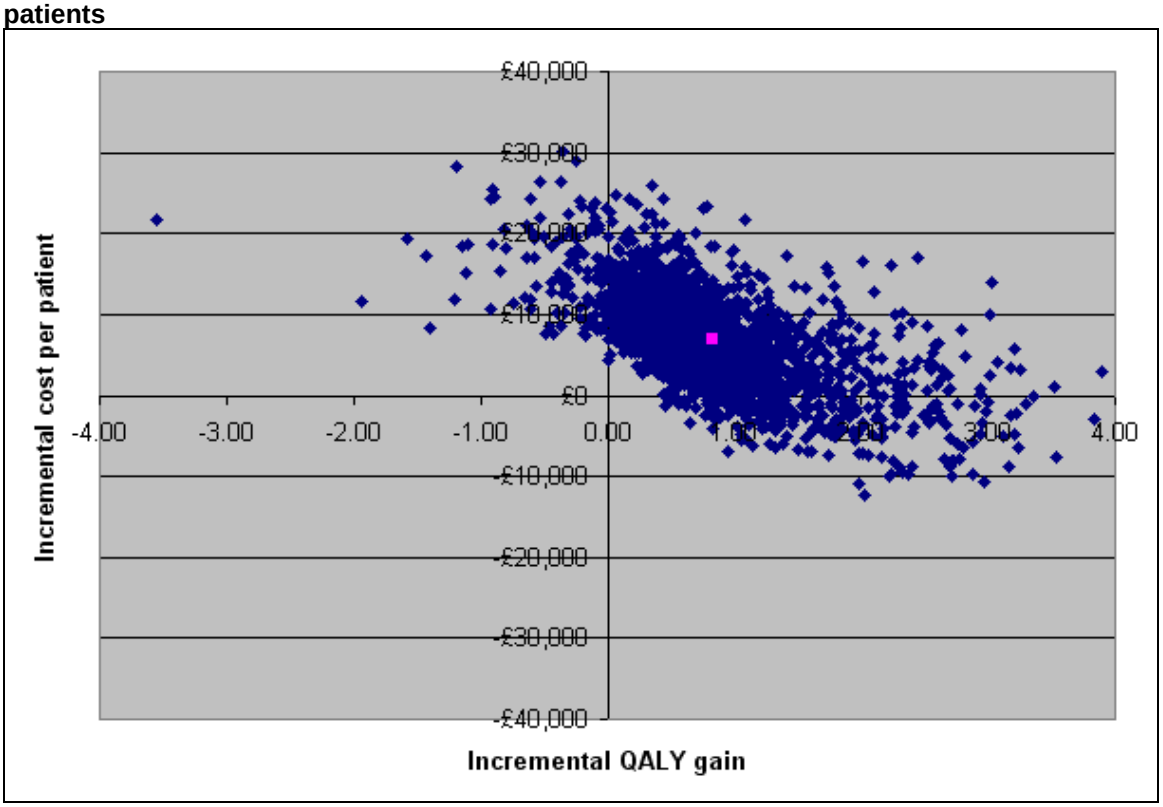
Only the main results of PSA are presented here. However, the spreadsheet model accompanying this submission enables PSA to be conducted on any plausible treatment strategy and allows generation of cost-effectiveness planes and curves for any pairwise or multiple-treatment comparisons.

Figure 9: Scattergraph/cost-effectiveness plane plotting the total lifetime cost per patient against the total number of QALYs per patient for each of the 20 treatments considered in PSA



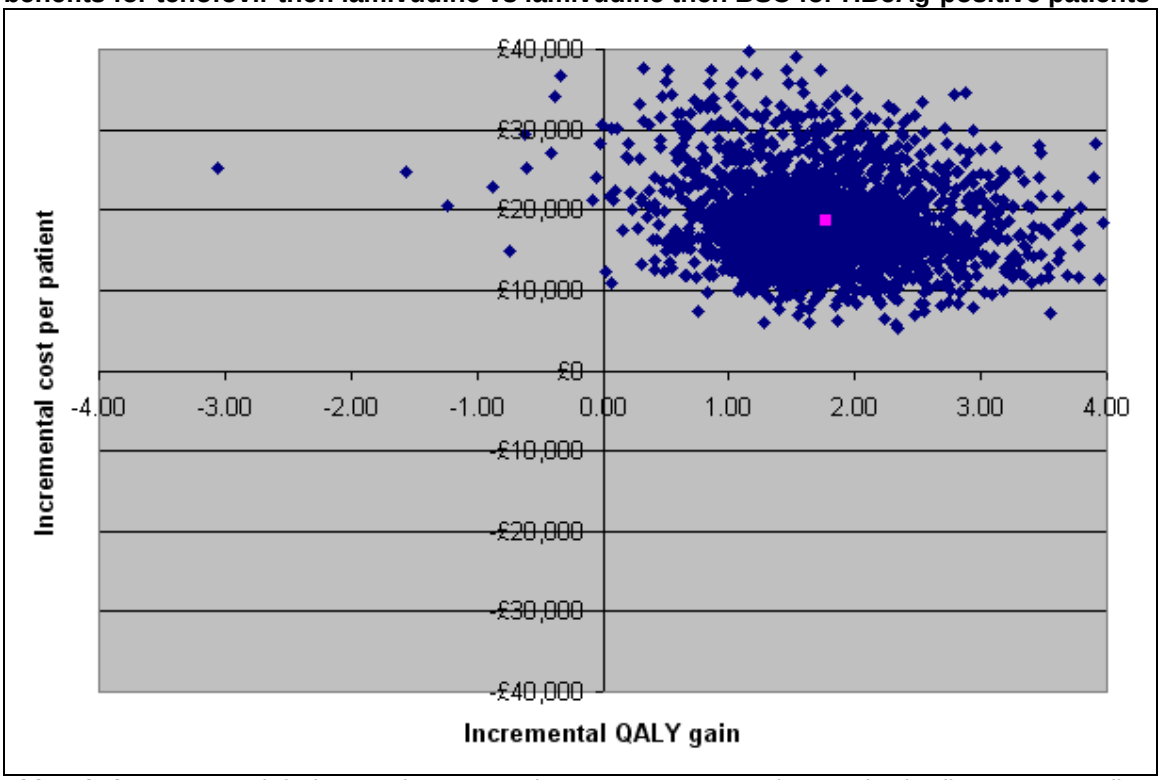
Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

Figure 10: Cost-effectiveness plane plotting the incremental costs against the incremental benefits for tenofovir then lamivudine vs lamivudine then tenofovir for HBeAg-positive patients



Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

Figure 11: Cost-effectiveness plane plotting the incremental costs against the incremental benefits for tenofovir then lamivudine vs lamivudine then BSC for HBeAg-positive patients



Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

PSA confirmed the findings of the base case analysis, demonstrating that first-line use of tenofovir is the most cost-effective strategy if the NHS has a "threshold" cost/QALY of £20,000-£30,000/QALY gained. However, all cost-effectiveness ratios were slightly higher than those calculated in the deterministic base case analysis: for example, the ICER for tenofovir then lamivudine relative to lamivudine then BSC is £10,577 (95% CI: £3,994, £50,251) per QALY gained in the PSA, compared with £7,344/QALY in the base case analysis (Table 42).

Table 42: Mean ICERs and 95% CI and probability of each treatment strategy being cost-effective at different ceiling ratios: HBeAg-positive patients.

	ICER TDF-LAM vs. treatment X			Probability of being most cost-effective (i.e. having highest net benefit)				
	Mean*	Lower 95% CI†	Upper 95% CI†	£0	£10,000	£20,000	£30,000	£50,000
BSC then BSC	£9,622	£3,124	£59,830	99.75%	29.25%	6.55%	2.75%	1.05%
LAM then TDF	£8,403	#	#	0.00%	26.65%	21.00%	11.85%	4.65%
TDF then LAM	-	-	-	0.00%	23.65%	35.90%	27.60%	18.40%
TDF then TDF+LAM	£26,074	#	£238,196	0.00%	1.05%	20.40%	33.10%	34.25%
TDF then TDF+LAM then ETV	£26,165	#	£240,042	0.00%	0.00%	3.30%	10.00%	21.95%
LAM then BSC	£10,577	£3,994	£50,251	0.25%	10.80%	2.05%	0.65%	0.05%
LAM then ETV	£3,048	#	£17,590	0.00%	0.00%	0.00%	0.00%	0.00%
LAM then ADV	£3,480	#	#	0.00%	7.85%	5.85%	4.35%	2.95%
ADV then LAM	Dominant	#	#	0.00%	0.25%	0.80%	0.65%	0.45%

	ICER TDF-LAM vs. treatment X			Probability of being most cost-effective (i.e. having highest net benefit)				
	Mean*	**Lower 95% CI†**	**Upper 95% CI†**	**£0**	**£10,000**	**£20,000**	**£30,000**	**£50,000**
LAM then TDF+LAM	£1,806	#	#	0.00%	0.00%	0.95%	3.05%	5.30%
TDF then BSC	£4,305	£885	£15,871	0.00%	0.30%	0.15%	0.10%	0.20%
TDF then ETV	Dominant	#	£243,155	0.00%	0.00%	0.10%	0.00%	0.05%
LAM then ADV+LAM	Dominant	#	£34,278	0.00%	0.05%	0.20%	0.25%	0.25%
ADV then TDF	Dominant	#	#	0.00%	0.00%	0.45%	0.80%	0.45%
ADV then TDF+LAM	Dominant	#	#	0.00%	0.00%	0.05%	0.20%	0.50%
ADV then ADV+LAM	Dominant	#	£141,944	0.00%	0.00%	0.00%	0.05%	0.05%
ETV then LAM	Dominant	#	£1,296,267	0.00%	0.05%	1.00%	1.85%	2.45%
ETV then TDF	Dominant	#	£1,261,105	0.00%	0.05%	0.60%	1.75%	5.20%
ADV+LAM then TDF+LAM	Dominant	#	£129,924	0.00%	0.05%	0.65%	1.00%	1.75%
ETV+ADV then LAM	Dominant	#	£3,098,753	0.00%	0.00%	0.00%	0.00%	0.05%
All first-line TDF strategies combined	-	-	-	0.00%	24.70%	59.60%	70.70%	74.60%
Cost-effectiveness frontier‡	-	-	-	99.75%	10.80%	35.90%	33.10%	34.25%

Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

Values shown in blue typeface indicate that the treatment(s) in question has/have the highest probability of being cost-effective at this threshold.

* The "mean" ICER is the ratio of the mean incremental costs and mean incremental QALYs.

† 95% CI were calculated using the percentile method, assigning all ICERs falling in the north-west quadrant (in which treatment is dominated by its comparator, being more costly and less effective) an arbitrarily high ICER.

The 95% CI was considered to be undefined as >2.5% of simulations lay in the south-west quadrant (in which treatment is less costly and less effective than its comparator) AND >2.5% lay in the north-east quadrant (in which treatment is more costly and more effective than its comparator).

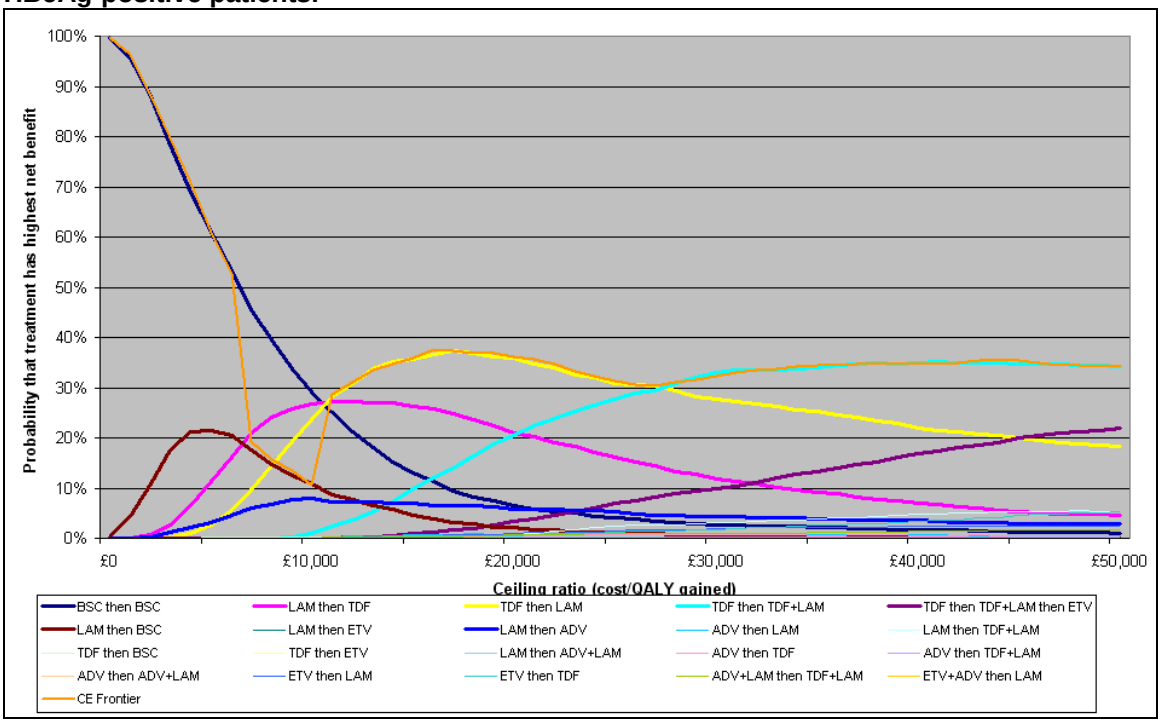
‡ The cost-effectiveness frontier represents the treatment with the highest expected net benefits at each ceiling ratio. The probabilities shown in this row represent the probability that the treatment with the highest expected net benefits is optimal. Error probabilities at any given threshold are equal to 1 minus the probabilities shown in this row.

For each of the 2,000 Monte Carlo simulations generated, the model calculated the net benefits for all 20 treatment strategies. These data were used to calculate the probability that (i.e. the proportion of simulations in which) each treatment is the most cost-effective treatment considered in the analysis at a range of different ceiling ratios showing possible values for our willingness to pay to gain one QALY (Figure 12 and Table 42).

This demonstrates that BSC is significantly less effective than all other treatment strategies considered in this analysis (p=0.004), in addition to having a >50% chance of being the optimal strategy at all ceiling ratios below £6,404.

Although it lies on the cost-effectiveness frontier in both the base case analysis and PSA, the probability that lamivudine then BSC is optimal never exceeds 21%. By contrast, lamivudine then tenofovir lies slightly above the cost-effectiveness frontier based on its mean costs and benefits within PSA (Table 42) but has a 27% probability of being optimal at a £10,000/QALY threshold.

Figure 12: Cost-effectiveness acceptability curves showing the probability that a particular treatment is the most cost-effective treatment considered in the analysis (i.e. has the highest net benefit) at a range of different threshold incremental cost-effectiveness ratios: HBeAg-positive patients.



Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

At a £20,000/QALY threshold, tenofovir followed by lamivudine had a 36% probability of being optimal, compared with 21% for lamivudine then tenofovir, 20% for tenofovir then tenofovir+lamivudine and 6% for lamivudine then adefovir. However, if the NHS were willing to pay £30,000 per QALY gained, tenofovir then tenofovir+lamivudine would have the highest probability of being cost-effective (33%). Tenofovir then lamivudine has the highest expected net benefits (and therefore lies on the cost-effectiveness frontier) at this threshold. The error probability at this threshold (one minus the probability that this treatment is optimal) is therefore 77%.

Pooling all strategies involving first-line use of tenofovir together demonstrates that we can be 60% confident that first-line use of tenofovir is the most cost-effective antiviral treatment for HBeAg-positive CHB if the NHS is willing to pay £20,000/QALY gained and 71% confident at a £30,000/QALY threshold.[3] Furthermore, there was a 57% probability that one of the first-line tenofovir strategies would be the most effective treatment considered in this analysis.

This analysis also demonstrated that the comparisons between different strategies including first-line tenofovir are extremely sensitive to model inputs: although at a £20,000/QALY ceiling ratio there is a 69% probability that lamivudine then BSC is cost-effective relative to BSC, a 68% probability that lamivudine then tenofovir is cost-effective relative to lamivudine then BSC and a 71% probability that tenofovir then lamivudine is cost-effective relative to lamivudine then tenofovir, the probability that

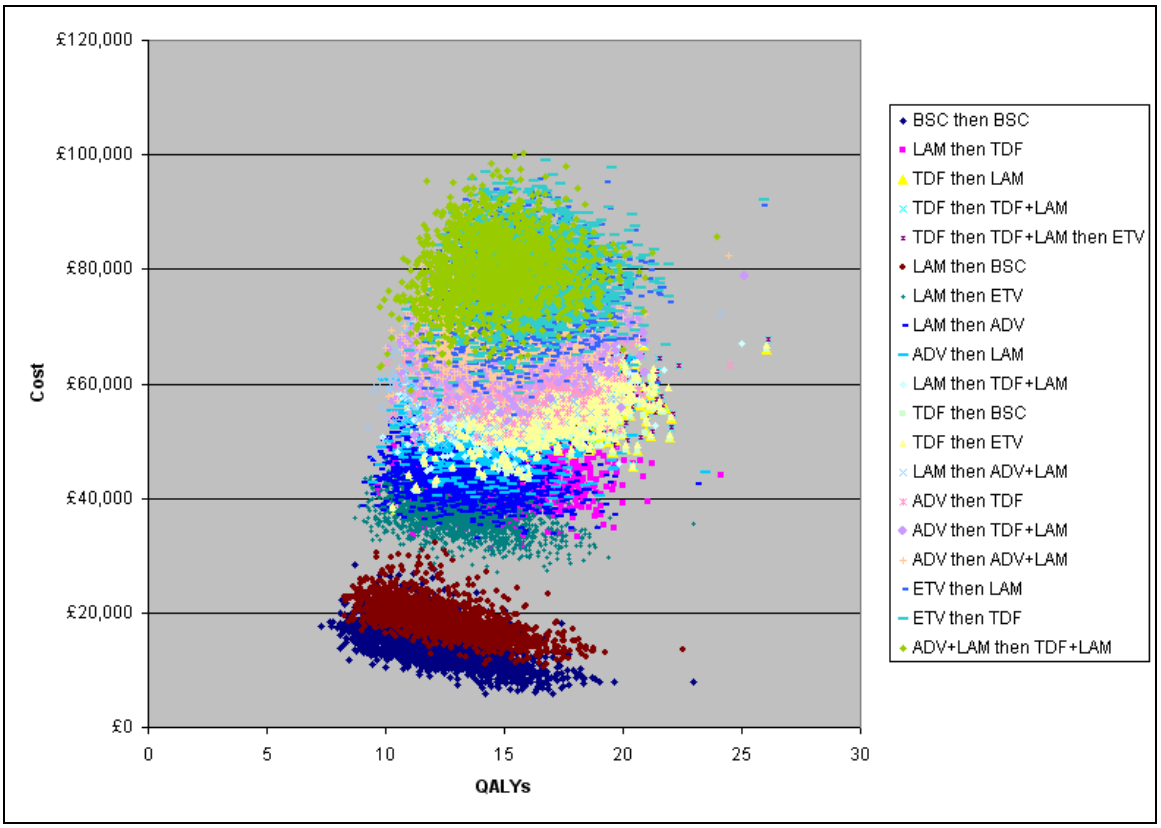
[3] If all first-line tenofovir strategies are treated as a single strategy, the error probability at a £20,000/QALY threshold is therefore 40%.

tenofovir then tenofovir+lamivudine is cost-effective relative to tenofovir then lamivudine is just 44% and the probability that tenofovir then tenofovir+lamivudine then entecavir is cost-effective relative to tenofovir then tenofovir+lamivudine is only 5%.

7.3.3.1.2. Probabilistic sensitivity analysis: HBeAg-negative patients

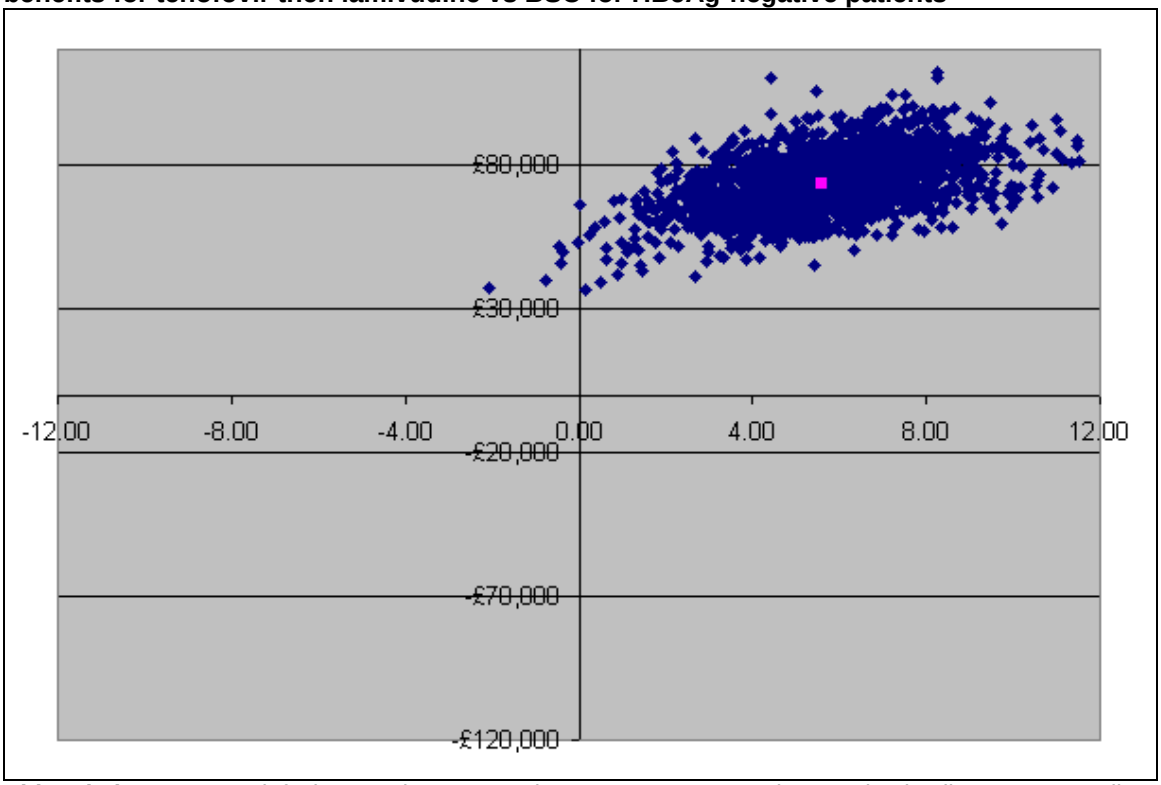
PSA was repeated for the HBeAg-negative population. The results for this population were strikingly similar to those for HBeAg-positive patients (Figure 12 and Figure 15).

Figure 13: Scattergraph/cost-effectiveness plane plotting the total lifetime cost per patient against the total number of QALYs per patient for each of the 20 treatments considered in PSA



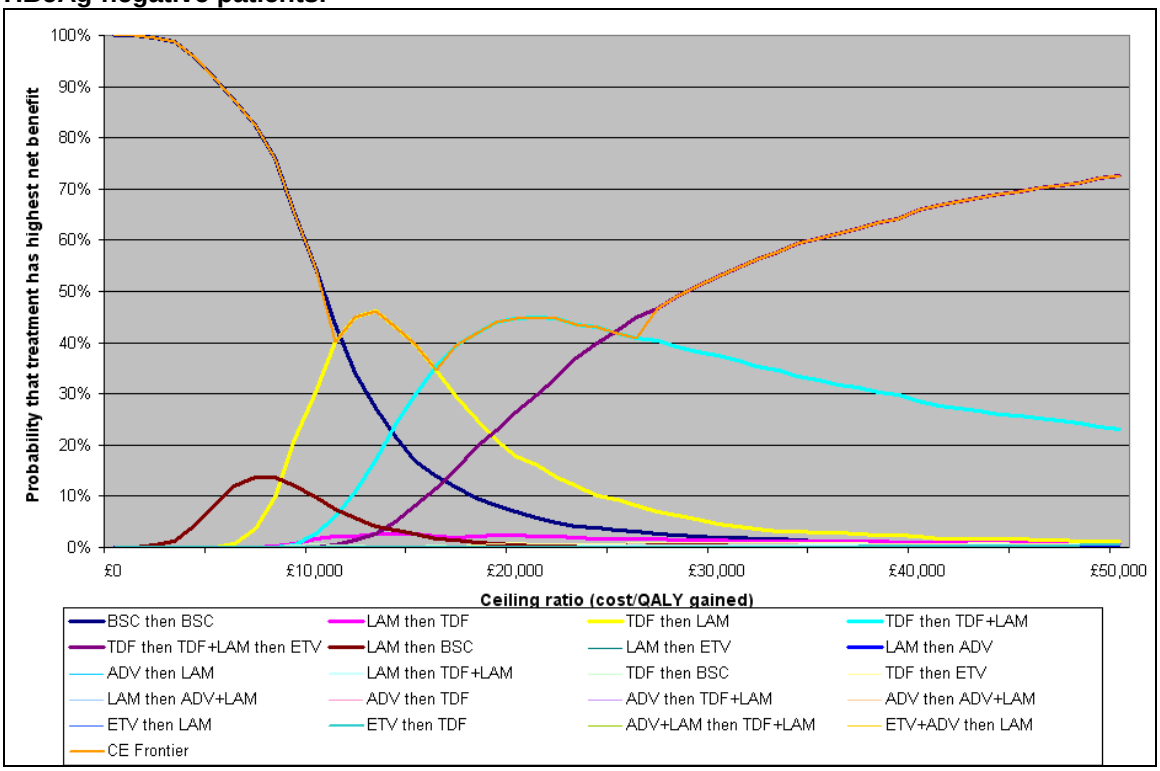
Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

Figure 14: Cost-effectiveness plane plotting the incremental costs against the incremental benefits for tenofovir then lamivudine vs BSC for HBeAg-negative patients



Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

Figure 15: Cost-effectiveness acceptability curves showing the probability that a particular treatment is the most cost-effective treatment considered in the analysis (i.e. has the highest net benefit) at a range of different threshold incremental cost-effectiveness ratios: HBeAg-negative patients.



Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

For HBeAg-negative patients, BSC had the highest probability of being cost-effective at all ceiling ratios below £11,200 and generated significantly fewer QALYs than any other treatment.

At a £20,000/QALY threshold, tenofovir then tenofovir+lamivudine had a 45% probability of being optimal, compared with 27% for tenofovir then tenofovir+lamivudine then entecavir, 18% for tenofovir followed by lamivudine, 7% for BSC and 2.3% for lamivudine then tenofovir. However, if the NHS was willing to pay £30,000 per QALY gained, tenofovir then tenofovir+lamivudine then entecavir would have the highest probability of being cost-effective (53%; Table 43).

Table 43: Mean ICERs and 95% CI and probability of each treatment strategy being cost-effective at different ceiling ratios: HBeAg-negative patients.

	ICER TDF-LAM vs. treatment X			Probability of being most cost-effective (i.e. having highest net benefit)				
	Mean	Lower 95% CI	Upper 95% CI	£0	£10,000	£20,000	£30,000	£50,000
BSC then BSC	£10,888	£6,432	£30,144	100.00%	54.60%	6.95%	2.00%	0.65%
LAM then TDF	£8,085	£3,872	£34,827	0.00%	1.70%	2.35%	1.40%	0.65%
TDF then LAM	-	-	-	0.00%	30.30%	17.80%	4.50%	1.20%
TDF then TDF+LAM	£16,083	£9,819	£47,066	0.00%	2.70%	44.70%	37.60%	23.10%
TDF then TDF+LAM	£16,108	£9,821	£47,176	0.00%	0.10%	26.55%	52.90%	72.65%

	ICER TDF-LAM vs. treatment X			Probability of being most cost-effective (i.e. having highest net benefit)				
	Mean	**Lower 95% CI**	**Upper 95% CI**	**£0**	**£10,000**	**£20,000**	**£30,000**	**£50,000**
then ETV								
LAM then BSC	£10,232	£6,462	£26,272	0.00%	9.80%	0.65%	0.40%	0.10%
LAM then ETV	£6,506	£3,780	£17,737	0.00%	0.00%	0.00%	0.00%	0.00%
LAM then ADV	£4,822	£2,414	£12,907	0.00%	0.00%	0.00%	0.00%	0.05%
ADV then LAM	£907	#	£6,822	0.00%	0.00%	0.00%	0.00%	0.00%
LAM then TDF+LAM	Dominant	#	£3,925	0.00%	0.00%	0.00%	0.25%	0.55%
TDF then BSC	£7,184	£4,532	£18,712	0.00%	0.80%	0.15%	0.00%	0.00%
TDF then ETV	£51,490	#	£577,408	0.00%	0.00%	0.85%	0.95%	0.55%
LAM then ADV+LAM	Dominant	#	£1,221	0.00%	0.00%	0.00%	0.00%	0.00%
ADV then TDF	Dominant	#	£34	0.00%	0.00%	0.00%	0.00%	0.00%
ADV then TDF+LAM	Dominant	#	Dominant	0.00%	0.00%	0.00%	0.00%	0.00%
ADV then ADV+LAM	Dominant	#	Dominant	0.00%	0.00%	0.00%	0.00%	0.00%
ETV then LAM	Dominant	#	£515,164	0.00%	0.00%	0.00%	0.00%	0.00%
ETV then TDF	Dominant	#	£1,378,639	0.00%	0.00%	0.00%	0.00%	0.50%
ADV+LAM then TDF+LAM	Dominant	#	Dominant	0.00%	0.00%	0.00%	0.00%	0.00%
ETV+ADV then LAM	Dominant	#	£3,037,118	0.00%	0.00%	0.00%	0.00%	0.00%
All first-line TDF strategies combined	-	-	-	**0.00%**	**33.10%**	**89.05%**	**95.00%**	**96.95%**
Cost-effectiveness frontier‡	-	-	-	**100.00%**	**54.60%**	**44.70%**	**52.90%**	**72.65%**

Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

Values shown in blue typeface indicate that the treatment(s) in question has/have the highest probability of being cost-effective at this threshold.
* The "mean" ICER is the ratio of the mean incremental costs and mean incremental QALYs.
† 95% CI were calculated using the percentile method, assigning all ICERs falling in the north-west quadrant (in which treatment is dominated by its comparator, being more costly and less effective) an arbitrarily high ICER.
# The 95% CI was considered to be undefined as >2.5% of simulations lay in the south-west quadrant (in which treatment is less costly and less effective than its comparator) AND >2.5% lay in the north-east quadrant (in which treatment is more costly and more effective than its comparator).
‡ The cost-effectiveness frontier represents the treatment with the highest expected net benefits at each ceiling ratio. The probabilities shown in this row represent the probability that the treatment with the highest expected net benefits is optimal. Error probabilities at any given threshold are equal to 1 minus the probabilities shown in this row.

We can be 89% confident that tenofovir is the most cost-effective antiviral strategy for managing HBeAg-negative CHB at a £20,000/QALY threshold (if all strategies involving first-line use of tenofovir are combined), which increases to 95% at a £30,000/QALY threshold. The error probability at a £20,000/QALY threshold is therefore 5% when all first-line tenofovir strategies are combined together. We can be 83% confident that one of the first-line tenofovir strategies would be the most effective treatment considered in this analysis.

As was the case for HBeAg-positive patients, the comparisons between different strategies including first-line tenofovir were extremely sensitive to model inputs: at a £20,000/QALY ceiling ratio there is a:

- 49% probability that lamivudine then BSC is cost-effective relative to BSC

- 91% probability that lamivudine then tenofovir is cost-effective relative to lamivudine then BSC
- 94% probability that tenofovir then lamivudine is cost-effective relative to lamivudine then tenofovir
- 73% probability that tenofovir then tenofovir+lamivudine is cost-effective relative to tenofovir then lamivudine
- 29% probability that tenofovir then tenofovir+lamivudine then entecavir is cost-effective relative to tenofovir then tenofovir+lamivudine.

Response appendix G:

Guide to the Tenofovir model

General information:

Throughout the model, all variables that can be amended are in yellow cells.
The only exceptions to this are the pages TP tables and TP tables (2) – No values on these sheets should be amended.

Throughout the model the treatment scenarios considered are defined with a row of 7 cells.
These cells contain numeric codes for the treatment considered first line, second line and third line and which transition tables should be used (i.e. the non-resistant or lamivudine resistant transition probability tables). See table 1 for an example of a defined scenario

Table 1: An example of a treatment scenario defined in the model

Treatment 1	Tx 1 - Lam Res	Treatment 2	Tx 2 - Lam Res	Treatment 3	Tx 3 - Lam Res	Switch to BSC
4	FALSE	9	FALSE	9	FALSE	TRUE

The numeric code corresponds to a treatment option defined in the model, table 2 defines which numeric value corresponds with which treatment option.

Table 2: Treatment code and corresponding treatment options

Treatment code	Treatment option
1	NA
2	Lamivudine
3	Adefovir
4	Tenofovir
5	Entecavir
6	Adefovir + lamivudine
7	Tenofovir + lamivudine
8	Entecavir + adefovir
9	BSC

The first four screens are for display purposes only.

Sheet - Starting states
This page defines the starting disease states of the patients in the first cycle of the Markov engine, **Tx 1 - Engine 1**

It also allows the user to define the number of patients considered in the model and to define which disease states can become resistance to therapy.

Sheet - Efficacy
This page defines the treatment specific transition probabilities. It also contains several relative risks and ratios.

All inputs on this page feed into the **TP Calcs** sheet which in turn calculates all of the transition probabilities that are used in the model, found on the **TP Tables (2)** sheet.

Sheet - Efficacy 2
This page defines all of the non treatment specific transition probabilities and several relative risks.

All inputs on this page feed into the **TP Calcs** sheet or directly into **TP Tables (2)** which in turn calculate all of the transition probabilities used in the model, found on the **TP Tables (2)** sheet.

Sheet TP Tables (2)
This page contains all of the transition probabilities used within the Markov engines.

There are 4 primary transition probability tables for each of the 8 treatment options considered in the mode, these are for:

- The first year of treatment – in non-resistant patients
- Subsequent years of treatment – in non-resistant patients
- The first year of treatment – in Lamivudine resistant patients
- Subsequent years of treatment – in Lamivudine resistant patients

There are 4 other tables for each treatment option that are used to model the year in which resistance develops and patients switch to alternative therapies.

All of the data on this page feeds into the **TP Tables** sheet which in turn links to the Markov engines.

Sheet – Resistance rates
This page contains the resistance rate data for the 8 treatment options considered in the model.

The resistance rates are provided for years 1, 2, 3, 4 and 5+ for both treatment naïve and patients that have already developed resistance to Lamivudine.

These values feed directly into the Markov engines.

Sheet – Costs
This sheet contains the drug costs and unit costs that are used to build up the disease state costs on the **Cost (2)** and **Cost Summary** sheets.

Sheets – Costs (2)
This page is used to generate the consultation costs associated with treatment. These calculations are based on the unit costs as provided on the **Costs (2)** sheet and direct inputs on the sheet.

These costs are used to build the disease state costs on the **Cost Summary** sheet.

Sheet – Cost Summary
This page gives the disease state costs used in the Markov engines of the model (i.e. the costs applied for each cycle that a patient remains in a defined disease state). These costs are calculated based on the **Cost (2)** and **Cost Summary** sheets.

This page also contains the discount rates that are applied within the model.

Sheet – Utilities
This page defines the disease state specific utility values used within the model (i.e. the utility value applied for each cycle that a patient remains in a defined disease state).

Sheet – Results
This page allows the user to define a treatment strategy and to see the results generated in the main Markov engines.

Any treatment scenario (see table 1) can be defined using the drop-down boxes that appear around cells E6:E8. It is also possible to define which transition tables should be used i.e. The user can manually choose to use the non-resistant or Lamivudine resistant transition probability tables, using the associated check-boxes.

This page also allows the user to define the time horizon to be considered in the model and whether to present the results with discounting and/or ½ cycle correction.

The results for the defined scenario appear in cells I12:L14.

This page also allows the user to compare 2 scenarios as defined and generated in the **Scenarios** sheet. Cells D16:G227 show the treatment options considered in each scenario. The user can define which two scenarios's to compare using the boxed section called Scenario Analyser.

Please note that the Scenario Analyser section only allows the user to view results generated on the **Scenarios** sheet. If amendments have been made to the model inputs then the results will need to be regenerated on the **Scenarios** sheet.

Sheet – Scenarios
This page allows the user to define the treatment strategies to be considered for deterministic analysis.

Columns E:K contain a numeric code for the treatment strategy considered and which transition tables should be used (i.e. the non-resistant or lamivudine resistant transition probability tables). Cells A32:B40 display which numeric value corresponds to which treatment option (i.e. If 4 is selected then the model uses the Tenofovir data)

Cells E6:K6 define the treatment strategy currently being considered and displays the associated results (i.e. Life years, QALYs and Costs) in cells M6:R6.

Clicking on the Generate Scenarios button will capture the deterministic results for each of the defined scenarios. The code loops the defined scenarios copying the each row (i.e. defined strategy) from columns E:K and pastes them into cells E6:K6. The associated results are then copied from cells M6:R6 next to the currently tested scenario in the rows below.
e.g. The macro will copy the cells E**8**:K**8** (scenario 1) and paste the values into E6:K6, the results for this scenario will then be copied from M6:R6 and pasted into M**8**:R**8**, corresponding to scenario 1. The macro then repeats this process incrementing the row values associated with the scenario.

There are several tables to the right of column R which summarise some of the results generated. It is also possible to view the results graphically, although this is a manual process.

The generated results can also be reviewed independently on the **Summary** sheet

Sheet – Analysis
This page allows the user to generate results for several scenarios where the initial starting disease states vary.

Clicking on the macro will copy the defined starting state scenarios in B35:B51 through to F35:B51 into the appropriate section of the **Stating state** sheet.

For each starting state scenario, the macro copies the defined treatment scenarios from cells B3:H3 and below into the **Scenario** sheet and captures the corresponding results which are then inserted into cells I3:N3 and below.

These results are then summarised in the cells I35:N79

Sheet – Scenario analysis
This page allows the user to vary one or more variables in the model and capture the results from 4 defined scenarios and then compare the results.

Column G contains a scenario value
Column H the variable title to be changed
Columns I & J the variable sheet and cell location
Column K the current value of the variable to be changed

Column L the variable value that is to be tested

When the user clicks on the generate table button the macro loops through the columns G:H. For each scenario value the macro will replace the default values with the defined value to be tested (e.g. on for the first scenario (1) the macro will change the discount rate of costs and outcomes to 0). The model will then copy the corresponding defined scenarios in columns N:T into the **Scenario** sheet and then capture the associated results from this sheet and paste them into columns U:Z in the corresponding location.

The macro will then replace the original variable values and repeat for the next scenario.

The results are then summarised in columns A:F

Sheet – TP Tables
This sheet is a duplicate of **TP Tables (2)** and is used by the Markov engines

Sheets – Tx 1 – Engine 1, Tx 2 Engine 1, Tx 3 Engine 1 and Summary Engine
These sheets are the Markov engines for the model.

These sheets use the treatment scenario defined on the Scenarios sheet cells E6:K6 to define which inputs from the model to use (i.e. which transition tables, resistance rates and costs).
The results of the model are summarised on both the **Scenario** and **Results** sheet.

Sheet – TP Calcs
This page uses the information entered into the **Efficacy** and **Efficacy 2** sheets to calculate the transition probabilities used within the Markov engines. The transition probabilities are presented on the **TP Tables (2)** sheet.

Sheet – Threshold analysis
This page allows the user to perform threshold analysis the cost effectiveness of two scenarios (using the Scenario and Scenario (2) sheet) on a number of model variables defined in columns M:O.

When the user clicks on the Threshold button the associated macro will use Excels Goal-seek function to determine what value the defined variables need to be to achieve a cost per QALY of £20,000 and £30,000 for the defined treatment scenarios. The results for the scenario are captured in columns U:V and need to be manually transferred into the appropriate section of the table D5:K15

Sheet – Data and references
This page contains all of the model variables.

It also contains the ranges for the variables allowing the user to generate a Tornado diagram and the distributions and associated randomly generated values which can be used in the probabilistic sensitivity analysis.

Clicking on the Tornado diagram button will insert the minimum and maximum values of each variable into the model and capture the associated impact on the value defined in cell I4 based on the scenario defined on this sheet (The scenarios are defined using the dropdowns on this screen). The associated results are present in columns K:N.

The Simulation button on the **Simulations** page will temporarily link all model variables to the probabilistically generated values in columns P:U.

Sheet – Tornado diagram
This page provides a graphical representation of the data generated using the Tornado diagram button on the **Data and references** sheet.

This graph shows the impact of varying each individual model variable in the model between a defined range on the **Data and reference** sheet.

Please note only the 20 data inputs which have the biggest impact are presented on this page.

Sheet – PSA Scenarios
This page simply defines the treatment scenarios to be tested in probabilistic sensitivity analysis on the **Simulations** page.

The number of scenarios considered is defined in the visual basic code (currently this is 20), however the ERG group now have an unlocked version of the model so can manually amend this figure.

It is possible to make this dynamic (i.e. only run for the number of scenarios defined without having to amend the code), if this would be of use please let Gilead know.

Sheet – Simulations
This page generates all of the probabilistic results for the 20 scenarios defined on the **PSA Scenarios** sheet.

When the user clicks on the Simulation button, the associated macro will link all model variables defined on the **Data and References** sheet to the associated probabilistically generated values on the same sheet, Column W.

The model will then generate X copies of the results defined by the figure in Cell D4, in the submission we ran 2,000 simulation.

To do this the model captures a set of probabilistically generated values from column U from the **Data and Reference** sheet and pastes it into Column W of the same sheet. The macro then loops through each of the scenarios defined on the **PSA scenarios** sheet, copying the treatment scenario definition into the **Scenarios** sheet and then copying the associated results into the simulation sheet. Once this has been done for all of the defined treatment scenarios the model will update the values in Column W of the **Data and reference** sheet and repeat until X simulations have been captured.

These results can then be compared both numerically and graphically. However, due to the variable number of simulations to be run and the impact updating calculations and graphs can have on the speed of running probabilistic sensitivity analysis these comparisons have to be entered manually once the results have been generated.

Please note: Due to the size and complexity of the model, generating probabilistic sensitivity analysis results can require a significant amount of processing time.

Sheet – CEAC
This page allows the user to compare two scenarios from the results generated on the **Simulations** sheet.

Use the dropdowns to select the two scenarios to compare.

The cost-effectiveness plane will automatically update, however manual manipulation of the axis scales and range plotted may be required to achieve an optimal representation.

The user will need to click on the Generate CEAC button to generate the cost-effectiveness acceptability curve for the selected comparison.

Sheet – CEACs

This page compares all of the PSA results for the treatment scenarios defined on the **PSA scenarios** sheet.

Due to the variable number of simulations that may be run the user must manually duplicate the formulas in cells A10:V10 down for the required number of rows (e.g. if 2,000 simulations have been generated the user must copy A10:V10 down to A2009:AV2009). This also needs to be done for cells AV10:BO10.

The ranges in the calculations within cells C6:V6 and C8:V8 will also need to be manually updated to reflect the ranges defined.

Once updated clicking on the Generate CEAC button will update the NET benefit CEAC graph shown on this screen.

Sheet – Scenarios (2)
This page is a duplicate of the **Scenario** sheet but is linked to alternative set of engines. This page allows the user to define an alternative treatment strategy to be considered for deterministic analysis.

The results presented on this allow comparisons of scenarios which are used for the Tornado diagrams and threshold analysis

Sheets – Tx 1 – Engine 1 (2), Tx 2 Engine 1 (2), Tx 3 Engine 1 (2) and Summary Engine 1 (2)
These sheets are a secondary set of Markov engines for the model and are duplications of the sheets **Tx 1 – Engine 1, Tx 2 Engine 1, Tx 3 Engine 1 and Summary Engine**.

However, these sheets use the treatment scenario defined on the **Scenarios (2)** sheet cells E6:K6 to define which inputs from the model to use (i.e. which transition tables, resistance rates and costs).

The results from these sheets allow comparisons of scenarios which are used for the Tornado diagrams and threshold analysis.