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Tenofovir disoproxil fumarate for the treatment of chronic hepatitis B

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Conflicts of Interest:

Dr Brook was the local lead in three multi-centre clinical trials sponsored by Gilead but did not receive any payment

[redacted]

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LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
ADV	Adefovir
ADV-TDF	Adefovir-Tenofovir
AE	Adverse event
AIC	Academic in confidence
ALT	Alanine aminotransferase
b.d.	Twice daily
BMI	Body mass index
BSC	Best supportive care
CC	Compensated cirrhosis
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CEF	Cost-effectiveness frontier
CHB	Chronic hepatitis B
CI	Confidence interval
CIC	Commercial in confidence
CPK	Creatine phosphokinase
CrI	Credible interval
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
DNA	Deoxyribonucleic acid
EASL	European Association for the Study of the Liver
EQ-5D	Euroqol 5 dimension
ERG	Evidence Review Group
ETV	Entecavir
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCHS	Hospital and Community Health Services
HCV	Hepatitis C virus

HDV	Hepatitis D virus
HIV	Human immunodeficiency virus
HTA	Health technology assessment
HUI	Health Utilities Index
ICER	Incremental Cost-Effectiveness Ratio
ITT	Intentions-to-treat
IVRS	Interactive voice response system
LAM	Lamivudine
TEL	Telbivudine
MS	Manufacturers submission
MTC	Mixed treatment comparison
NHS	National health service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NR	Not reported
o.d.	Once daily
OR	Odds ratio
PCR	Polymerase chain reaction
QALY	Quality-adjusted life year
RAT	Randomised and treated
RCT	Randomised controlled trial
SAE	Serious adverse event
SD	Standard deviation
SHTAC	Southampton Health Technology Assessments Centre
SF-36	Short form health survey
SMC	Scottish Medicines Consortium
TAR	Technology Assessment Report
TDF	Tenofovir disoproxil fumarate
TDF-TDF	Tenofovir-Tenofovir
TTO	Time Trade Off
UKCRN	UK Clinical Research Network
ULN	Upper limit of normal
vs	Versus

VS	Viral suppression

SUMMARY

Scope of the submission

The manufacturer's submission (MS) generally reflects the scope of the appraisal issued by the National Institute for Health and Clinical Excellence (NICE), and is appropriate to the National Health Service (NHS). The decision problem deviates slightly from the scope in the following areas:

- The MS assessment of clinical-effectiveness includes the drug combination tenofovir plus emtricitabine (Truvada, Gilead). As this is not licensed for chronic Hepatitis B (CHB), the Evidence Review Group (ERG) considers it to beyond the scope of the appraisal.
- The MS does not consider three of the comparators listed in the scope: interferon alfa-2a, interferon alfa 2-b and pegylated interferon alfa-2a. However the manufacturer justifies this decision and the ERG agrees it is appropriate.

Summary of submitted clinical-effectiveness evidence

The evidence in the MS comes from three international randomised controlled trials (RCTs) and a mixed treatment comparison (MTC) using Bayesian methodology.

- Two RCTs compared tenofovir with adefovir [one in Hepatitis B e antigen (HBeAg) positive patients, one in HBeAg negative patients], and a third RCT compared tenofovir with tenofovir plus emtricitabine. The latter RCT is considered by the ERG to be beyond the scope of the appraisal and not considered further.
- The primary outcome, 'complete response', was a composite endpoint defined as histology response (≥ 2-point Knodell necroinflammatory score without worsening in fibrosis) and hepatitis B virus deoxyribonucleic acid (HBV DNA) below 400 copies/mL. For both HBeAg positive and HBeAg negative patients, a significantly greater proportion had a complete response after 48 weeks with tenofovir than with adefovir.
- There was no statistically significant difference in histologic response in either group of patients compared with adefovir.
- In both HBeAg positive and HBeAg negative patients, significantly more patients receiving tenofovir than adefovir had reductions in HBV DNA levels below 400, 300 and 169 copies/mL, and the mean reduction from baseline in plasma HBV DNA was significantly greater with tenofovir than adefovir.

- In terms of secondary outcomes, there were statistically significant differences between tenofovir and adefovir in alanine aminotransferase (ALT) response (although no difference in the proportion of HBeAg negative patients with normalised ALT levels at 48 weeks). A similar proportion of HBeAg positive patients experienced HBeAg loss and seroconversion at week 48 in the tenofovir and adefovir groups. No HBeAg negative patients experienced HBsAg loss or seroconverted to anti-HBs by week 48. Significantly more HBeAg positive patients achieved HBsAg loss at 48 weeks with tenofovir than with adefovir.
- No cases of virologic HBV resistance have been identified.
- There were no statistically significant differences between tenofovir and adefovir in overall adverse events in either subgroup of patients, although in HBeAg positive patients, there was a greater incidence of study drug-related adverse events with tenofovir. The MS attributes this to a higher incidence of mild nausea in the tenofovir treatment group. The most common adverse events were headache, nasopharyngitis, back pain, nausea, fatigue and abdominal pain.

An MTC was conducted on two outcomes: the probability of HBeAg seroconversion and the probability of achieving HBV DNA <300 copies/mL after one year of treatment.

- Of four subgroups considered, results could only be generated for HBeAg positive nucleos(t)ide naïve patients (n=13 RCTs). There was insufficient RCT evidence to construct an MTC for HBeAg negative nucleos(t)ide naïve patients, or HBeAg positive or negative lamivudine refractory patients.
- The probability of achieving undetectable HBV DNA with tenofovir was found to be significantly higher than that for all other treatments considered in the analysis at the 0.05 level. The analysis demonstrated that there is a 98% probability that tenofovir is the most potent nucleos(t)ide in terms of this outcome. All treatments were associated with a significantly higher chance of achieving undetectable HBV DNA than placebo. Tenofovir, entecavir and telbivudine were also found to be significantly superior to lamivudine at the 0.05 level.
- All treatments other than telbivudine + lamivudine in combination were found to significantly increase the probability of HBeAg seroconversion at one year relative to placebo at the 0.05 level. However, this analysis identified no statistically significant differences between the nucleos(t)ides for this outcome.

Summary of submitted cost-effectiveness evidence

- The cost-effectiveness analysis has adopted a Markov state transition model to estimate the incremental costs and consequences of a range of treatment strategies which include tenofovir and other anti-viral drugs. Evidence on the efficacy of tenofovir, lamivudine, adefovir and entecavir (alone or in combination, where appropriate) in terms of reducing viral load and HBeAg seroconversion were taken from the MTC which also estimated baseline outcomes for best supportive care (BSC) (based on outcomes in the placebo arms of included RCTs). These outcomes are associated with reduced probability of progression to advanced liver disease and may also be associated with improved quality of life.
- The model was used to simulate cohorts of patients with HBeAg positive and HBeAg negative CHB, at treatment initiation, separately. The model was structured to allow HBeAg negative CHB to emerge in HBeAg-positive patients, following reactivation of disease in patients who had achieved HBeAg seroconversion. In all other respects the model was structurally similar to those adopted for previous economic evaluations, including that used in the previous NICE assessment of adefovir for the treatment of CHB.
- The model adopted a lifetime horizon and was used to extrapolate lifetime costs and QALYs for patients treated with tenofovir (alone or in combination) and each of the included comparators. The analysis assumed that, once patients develop resistance to their current anti-viral drug they will either switch to a new drug or add a new drug to their treatment. The model was used to evaluate single-agent and combination therapies adopted as first-, second- or third-line treatment with BSC retained as the final treatment option for patients who have developed resistance to all anti-viral agents available in each treatment strategy. Of the 211 treatment strategies evaluated (including BSC) cost-effective strategies were selected using the cost-effectiveness frontier and incremental cost-effectiveness ratios (ICERs) calculated against the next best alternative.
- The MS concludes that tenofovir is a cost-effective option as first-line treatment. For HBeAg positive patients, tenofovir followed by lamivudine has an ICER of £9,940 per QALY gained, compared with lamivudine followed by tenofovir. This implies switching treatments on development of resistance to first-line therapy, which is not supported by clinical guidelines as an appropriate clinical strategy. A more appropriate treatment strategy of tenofovir followed by tenofovir plus lamivudine has an ICER of £10,055 per QALY gained, compared with lamivudine followed by tenofovir.

- The MS reports that for HBeAg negative patients, tenofovir followed by lamivudine has an ICER of £9,811 per QALY gained, compared with BSC. A more clinically appropriate treatment strategy of tenofovir followed by tenofovir plus lamivudine has an ICER of £13,854 per QALY gained, compared with tenofovir followed by lamivudine.

Commentary on the robustness of submitted evidence

Strengths

- The two tenofovir RCTs were of good methodological quality and measured outcomes that are appropriate and clinically relevant, although health related quality of life was not reported.
- The MS provided a detailed account of their procedures for the MTC, although much of this is reported in an academic in confidence (AIC) appendix.
- The economic model is structurally consistent with models adopted for previous economic evaluations. The MS reports that the structure of the model was discussed with clinicians with relevant expertise.
- The methods used to derive input data for the economic model are generally appropriate using published data which, for the MTC and pooled analysis of resistance, are clearly identified.
- The model is appropriately structured to incorporate resistance to anti-viral agents, and to maintain patients history of resistance to agents within a given treatment strategy.

Weaknesses

- The MS conducted a systematic search for clinical and cost-effectiveness studies of tenofovir and comparator treatments for CHB. However, some of NICE's recommended databases were not searched, and the search is only current to August 2007. ERG replication of the searches (PubMed only) from August 2007 to December 2008 have not identified any additional tenofovir RCTs.
- Whilst considered generally sound in terms of structure, the MTC suffers from certain limitations, including small numbers of studies / single studies in some networks, no quality assessment of the included studies, and no discussion of potential clinical heterogeneity.
- The ERG has uncovered a number of errors in the submission. These include transcription errors (from the model into the written submission) and errors in calculations in the model.

Where possible the ERG has corrected these errors and re-run the analyses. However, some of the errors would require substantial re-writing of the model, which is beyond the scope of this report. The ERG has attempted to identify where errors are likely to bias the outcome of the evaluation and concentrate on those errors.

- The reporting of pre-model analyses is poor, particularly in terms of searching for and critical appraisal of studies used to estimate parameter inputs. In many cases very limited information is provided on studies contributing data to key input parameters in the model. There is generally little evidence of systematic searches for data to estimate parameters and no critical appraisal of the scope, quality or appropriateness of included studies

Areas of uncertainty

- There is a lack of head-to-head RCT evidence for the clinical-effectiveness of tenofovir compared to other nucleos(t)ides. It was only possible to construct an MTC, taking into account direct and indirect RCT evidence, for HBeAg positive treatment naïve patients.
- Pre-model analysis of key input parameters to the model was hampered by sparsity of data. The submission has tended to use measures of uncertainty for input parameters that are based on statistical analyses (for example, standard deviations or standard errors) which will not reflect the true degree of uncertainty in estimating these parameters.

Key issues

- Tenofovir monotherapy has a favourable resistance profile, based on currently available evidence. Long-term resistance data are awaited, and when available will guide decisions regarding whether monotherapy or combination therapy should be given. Further RCT data on the clinical-effectiveness of nucleos(t)ide combination therapy is needed to support such decisions.

1 Introduction to ERG Report

This report is a critique of the manufacturer's submission (MS) to NICE from Gilead Sciences on the clinical-effectiveness and cost-effectiveness of tenofovir for CHB. It identifies the strengths and weakness of the MS. Clinical experts were consulted to advise the Evidence Review Group (ERG) and to help inform this review.

Clarification on some aspects of the MS was requested from the manufacturer by the ERG via NICE on 10-11-2008. A response from the manufacturer via NICE was received by the ERG on 28-11-08 and this has been included as an appendix to the ERG report. The manufacturer submitted a revised version of the MS which was received by the ERG on 1-12-08. The revised MS incorporates some changes made in response to the ERG's clarification questions (all changes highlighted in red in the revised MS).

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The overview of the disease description is generally accurate and clear. The MS states that the largest estimate figures for CHB suggest that it affects about 326,000 people in the UK, citing a Hep B Foundation report as the source of this figure (MS sections 3 and 4.1).[1] (although the actual figure quoted in the Hep B Foundation report is 325,000). The MS suggests that the number of new cases per year (7,700) may be an underestimate of the impact of recent migration and the ERG concurs.

2.2 Critique of manufacturer's overview of current service provision

The MS provides a generally accurate and clear overview of current service provision. The MS suggests that there is a degree of uncertainty regarding current best practice in relation to choice of drug (MS section 5.1), especially around the efficacy of newer nucleos(t)ides, and that there is a lack of consensus around treatment pathways (MS section 4.5). Generally, the clinical experts consulted by the ERG agree with this.

The MS states that lamivudine is the most commonly used first line treatment in nucleoside-naïve CHB patients in the UK, with the addition of adefovir as rescue therapy upon emergence of viral resistance (or lamivudine/adefovir combination therapy) (MS section 4.5). It is suggested that an increasing number of clinicians now use tenofovir or tenofovir plus lamivudine first-line (MS section 4.5). The MS proposes the most plausible drug combinations, in terms of minimising the risk of cross-resistance, as being lamivudine plus adefovir, lamivudine plus tenofovir and adefovir plus entecavir (MS section 3). Expert clinical opinion agrees that these combinations are appropriate, and note that initiating therapy with tenofovir in combination with another nucleos(t)ide would have potential advantages in terms of reducing the likelihood of cross-resistance, particularly as long-term data on resistance to tenofovir monotherapy is not yet available. However, initiating therapy with combination therapy may not be the preference of all clinicians.

The MS states that there is a shortage of RCTs evaluating combinations of two or more nucleos(t)ides, hence there is uncertainly around the benefits of combination therapy and the ERG agrees with this statement (MS section 4.5). The MS also points out that there is little evidence at present about the most effective treatments in patients resistant to drugs other than lamivudine, with clinicians varying in their choice of second-line treatment (MS section 4.5). The ERG concurs. The MS states that forthcoming European Association for the Study of the Liver (EASL) guidelines recommend that tenofovir (or entecavir) monotherapy can be used as first-line monotherapy for the treatment of CHB.[2] However, the guidelines also recommend that long-term monotherapy should be reconsidered if higher rates of resistance occur.

2.3 Critique of manufacturer's definition of decision problem

2.3.1 Population

The population described in the decision problem is adults with active CHB (evidence of viral replication and active liver inflammation) and compensated liver disease. This matches the scope for the appraisal, the licensed indication, and is appropriate for the NHS. Unlike the scope and the decision problem, the MS included some studies containing varying proportions of patients co-infected with human immuno-deficiency virus (HIV). (see section 3.1.2)

In accordance with the scope, the decision problem distinguishes between subgroups of patients, namely treatment naïve HBeAg positive and negative patients, and lamivudine resistant HBeAg positive and negative patients.

2.3.2 Intervention

The description of the intervention reflects the decision problem, its use in the UK and is appropriate for the NHS. All of the studies included in the MS used the licensed UK dose of tenofovir.

2.3.3 Comparators

The scope included interferon alfa-2a/2b, pegylated interferon alfa-2a, lamivudine, adefovir and entecavir as comparators. The MS included lamivudine, adefovir and entecavir as comparators but not interferon alfa-2a/2b and pegylated interferon alfa-2a as the manufacturer suggests that they are generally reserved for a smaller selected group of patients. The ERG concurs (see section 3.1.2). Telbivudine, although not included in the scope and the decision problem, is included as a comparator in the MTC (but not the economic model). NICE currently does not recommend telbuvdine for the treatment of CHB in England and Wales. [3] The manufacturer states that including RCTs of telbivudine facilitates the network of evidence needed to build an MTC. As RCTs of telbivudine have tended use lamivudine or adefovir as comparators this seems a reasonable justification, but it should be acknowledged that telbivudine is nonetheless outside the scope of the appraisal and the comparisons with this drug made by the manufacturer should be disregarded.

2.3.4 Outcomes

The outcomes selected by the manufacturer are appropriate and they match the NICE scope/decision problem. There are no other clinically relevant outcomes that appear to have been omitted from the decision problem. However, some of these outcomes were not reported in the included RCTs or the MTC (see section 3.1.4).

2.3.5 Economic analysis

The economic analysis in the decision problem is considered to be appropriate for the NHS. Under 'other considerations' in the decision problem, the manufacturer states 'the economic evaluation will consider only licensed treatment options used in accordance with their licensed indications, although patients will be assumed to continue therapy after hepatic decompensation'. Although hepatic decompensation is not a therapeutic indication for tenofovir, the ERG agrees that continued treatment after hepatic decompensation is appropriate. (see section 4.3.1)

2.3.6 Subgroups

The MS presents a subgroup analysis for cirrhotic patients and lamivudine experienced patients (i.e. previously treated for more than 12 weeks) in both study 0102[4] and 0103[5]. It is important to consider these subgroups as response to treatment may differ according to the presence of advanced liver disease, and those who have already been treated with lamivudine. These may be post-hoc analyses, as they were published as conference presentations and do not appear in the clinical study reports. The subgroup analyses potentially may be underpowered as they contain relatively small proportions of patients (around 20% for cirrhotic patients, and 10% for lamivudine experienced patients).

3 CLINICAL-EFFECTIVENESS

3.1 Critique of manufacturer's approach to systematic review

3.1.1 Description of manufacturer's search strategy

Overall the search was reasonably adequate but there were some limitations as outlined below.

3.1.1.1 Clinical-effectiveness searches

Sources

Embase was not recorded as searched in the MS, failing to meet the minimum database criteria in the NICE guide to manufacturers. Pubmed was searched, covering the prerequisite to search Medline and MEIP. Clarification with the manufacturers established that The Cochrane Central

Register of Controlled Trials was not searched, although all other Cochrane Library databases had been (see Appendix). The impact on the results of having not searched Embase is unknown. The ERG has not replicated the manufacturer's search strategy for this database.

Strategy

The Pubmed search strategy given in MS Appendix 2 was a list of free text terms with one index term for Hepatitis B. It did not contain an RCT search filter and had no record of how the terms were linked, nor the number of hits retrieved. The terms chosen, however were appropriate. The full Pubmed search strategy was requested from the manufacturer (see Appendix). The total number of hits (n=1057) was recorded without the individual hits per lines being noted. The Cochrane Library search used only the treatment terms. The numbers of records retrieved from this database was not recorded.

Limits

Searches for entecavir, telbivudine and tenofovir were not subject to any limits by date, whereas searches for adefovir and lamivudine were restricted to 1st July 2004, placing a reliance on the results from systematic reviews undertaken previously on these drugs for the NICE / Scottish Medicines Consortium (SMC) appraisal of adefovir. The search was limited to humans but was not limited by language. The Pubmed search was conducted on the 31st August 2007 and an update search was not run.

The ERG ran an update search using the MS strategy on Pubmed. Although this search did not identify additional RCTs of tenofovir relevant to the MS, examination of the titles and abstracts suggested that there were nine potentially relevant trials [6-14] of the comparator nucleos(t)ides. As these have not been screened according to the manufacturer's inclusion / exclusion criteria their relevance to the submission is uncertain. One of the nine RCTs is a full journal article evaluating adefovir and lamivudine combination therapy.[13] The MS only included a 2003 conference abstract for this trial and there are some discrepancies between the data in the abstract and the journal article (see section 3.1.6).

Other Sources used in the MS

Further data sources used in the MS were "manufacturer/conference websites and published review articles after this date" and regulatory submissions. Unpublished and on-going research were identified through in-house sources of information, hand searching, citation chasing,

conference proceedings specifically from the American Association for the Study of Liver Diseases (AASLD) 2007 conference and New Drug File. Promedis, the producers of New Drug File were contacted for information about their sources. It would appear to provide top-line industry news on products, competitors, trials and launch information opposed to containing bibliographic records, so it is unlikely to be the best source for conducting systematic reviews.

The ERG checked the following sources to look for additional ongoing trials: clinical trials.gov, and the UK Clinical Research Network (UKCRN). One relevant RCT of tenofovir was identified: 'Entecavir plus tenofovir combination therapy versus entecavir monotherapy in naive subjects with chronic Hepatitis B'. Sponsor: Bristol-Myers Squibb. Phase III RCT. NCT ID: NCT00410072. Other IDs: AI463-110. Start Date: April 2007. Completion Date: September 2011. http://clinicaltrials.gov/ct2/show/NCT00410072.

3.1.1.2 Cost-effectiveness searches

The number of references identified for clinical and cost-effectiveness studies could not be individually recorded on account of the single search combining clinical and cost results with no filters applied (see MS section 6.1, Figure 1; MS section 7.1; MS Appendix 2, Figure 1). A cost filter was not used in the strategy. The ERG was therefore unable to replicate the cost-effectiveness search to check the numbers reported. The search was run on the 31st August 2007 with no record of an update search being conducted. Pubmed and the Cochrane Library were recorded as searched and clarification with the manufacturer indicated that the NHS Economic Evaluation Database (NHS EED) had been included in the Cochrane Library search (see Appendix). Other sources searched were in-house data on file, contact with clinicians, citation chasing from reviews, and abstracts presented at AASLD 2007 and EASL 2008 (MS section 7.1.1).

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection

The MS provides only a summary of the inclusion criteria for the systematic review (MS section 6.1), while the full criteria can be found in an appendix (MS Appendix 2). There was no restriction on language, but studies were excluded if there was no English translation from the British Library.

The MS states that the inclusion criteria for the MTC were more stringent to ensure only comparable studies were combined statistically. Again, only a summary is provided in the report (MS section 6.6). The full inclusion criteria are reported in an AIC appendix (Appendix 4).

Interferon alfa-2a and 2b, as well as pegylated interferon alfa-2a were not considered by the MS as comparators, but were present in the scope. The ERG agrees with the MS justification for the omission, in that these drugs are generally reserved for a small selected subgroup of patients, usually HBeAg positive, who are considered able to tolerate interferon, and in whom the primary aim is to achieve HBeAg seroconversion. The interferons are therefore not considered as a direct alternative to tenofovir.

The scope stated that co-infected patients [HIV, Hepatitis C virus (HCV) or Hepatitis D virus (HDV)] should not be specifically considered. The MS permitted inclusion of tenofovir RCTs with less than 50% of HIV co-infected patients in the total study population. It is not clear why this threshold was chosen. Expert clinical opinion suggests that outcomes such as HBeAg seroconversion, HBsAg seroconversion and ALT normalisation (but not HBV DNA) may differ according to the presence of concomitant HIV infection, although there are few studies which have confirmed this.

The MS specified no limits relating to the quality or setting of the included RCTs. The RCTs included in the systematic review were set in North America, Europe, and Australia/New Zealand, with only two centres in the UK. Expert opinion suggests that clinical practice in these countries is similar, although treatment in the USA may commence earlier. The RCTs therefore reflect the nature of the decision problem stated in the submission, the licensed indication and are relevant to the NHS.

3.1.2.1 Identified studies

The MS provided a flow diagram in section 6.1 showing the process of study identification. However, the figure was ambiguous so clarification was sought from the manufacturer. The amended figure indicated that 1272 citations were identified by electronic and hand searches, plus a further 25 studies identified by a previous systematic review conducted by the manufacturer for the NICE appraisal of adefovir (see Appendix). A total of 77 RCTs and 46 non-

randomised studies met the inclusion criteria for the "wider systematic review". Of the 77 RCTs, 23 met the inclusion criteria for the MTC. A bibliography of 54 RCTs excluded from the MTC, together with reasons for exclusion, was provided by the manufacturer following a request from the ERG (see Appendix). The MS did not state whether inclusion/exclusion criteria were applied to each reference by more than one person.

The manufacturer's assessment of clinical-effectiveness essentially focuses on three pivotal tenofovir RCTs (MS section 6).[4,5,15] Of these, one trial compared tenofovir versus a fixed-dose combination of emtricitabine plus tenofovir.[15] Emtricitabine is not licensed for the treatment of CHB and the ERG does not consider that this study meets the NICE scope. This study has therefore not been assessed by the ERG and will not be discussed any further in this report.

Of the two remaining RCTs identified as study 0102[4] and study 0103[5] (both sponsored by the manufacturer), both compared tenofovir to adefovir. The population of study 0102[4] consisted of chronic treatment-naïve HBeAg-negative patients, while that of study 0103[5] consisted of chronic treatment-naïve HBeAg-positive patients. Subsequent to the MS, a journal article based on studies 0102[4] and 0103[5] has now been published.[16]

The manufacturer provided electronic copies of the full CIC clinical trial reports, averaging around 2000 pages per trial including references (N.B The ERG has not systematically assessed these reports), together with a linked EASL conference abstract. Although some resistance data was published in the abstract in 2008, all of the resistance data in the full trial reports was marked as commercial-in-confidence (CIC). After seeking clarification from the manufacturer, it emerged that the resistance data from the abstract was marked CIC in the MS in error (MS section 6.10.1.4).

The ERG does not suspect that any key trials have been excluded from the MS, although a systematic check of the list of excluded trials has not been undertaken.

CONSORT flow charts were presented only for the three trials presented in the MS assessment of clinical-effectiveness.[4,5,15] In addition, only these trials received a full quality assessment. Summary information of the RCTs is provided in tables detailing interventions (MS Table 2), population (MS Table 2), trial methods and designs (MS Table 5), as well as outcomes (MS Table 10). The characteristics of the included RCTs can be seen in Table 1.

Table 1 Characteristics of the included RCTs

Methods	Participants	Outcomes
Study GS-US-174-0102[4] *Design:* phase III, multi-centre double-blind RCT *Interventions*: Grp1: TDF 300 mg o.d. Grp2: ADV 10 mg o.d. *Number of centres*: 79 sites in 15 countries (2 UK sites) worldwide *Duration*: 48 weeks *Length of follow-up:* open-label TDF 300 mg o.d. to wk 384	*Participant numbers: n* = 375 Grp1: TDF *n* = 250 Grp2: ADV *n* = 125 *Key Inclusion criteria*: Adults (18-69) with active HBeAg-negative chronic HBV infection, and: • nucleoside naïve • positive serum HBsAg for ≥ 6mths • HBV DNA >10^5 copies/mL • ALT > ULN, ≤ 10× ULN • liver biopsy within last 6mths (with compatible histology of CHB)	*Primary endpoint:* proportion achieving a composite virological and histologic response *Secondary endpoints:* HBV DNA, virology, histology, ALT levels
Study GS-US-174-0103[5] *Design:* phase III, multi-centre double-blind RCT *Interventions*: Grp1: TDF 300 mg o.d. Grp2: ADV 10 mg o.d. *Number of centres*: 90 sites in 15 countries (3 UK sites) worldwide *Duration*: 48 weeks *Length of follow-up:* open-	*Participant numbers: n* = 266 Grp1:TDF *n* = 176 Grp2: ADV *n* = 90 *Key Inclusion criteria*: Adults (18-69) with active HBeAg-positive chronic HBV infection, and: • nucleoside naïve • positive serum HBsAg for ≥ 6mths • HBV DNA >10^6 copies/mL • ALT >2 x ULN, ≤ 10× ULN • liver biopsy within last 6mths (with compatible histology of CHB)	*Primary endpoint:* proportion achieving a composite virological and histologic response *Secondary endpoints:* HBV DNA, virology, histology, ALT levels, proportion of RAT participants with HBeAg loss or seroconversion to anti-HBe

label TDF 300 mg o.d. to wk 384		

ULN = Upper limit of normal

The MS reports that there were different frequencies of HBV genotypes in the trials compared with those observed in England and Wales. However, it is noted that this should have no significant impact on the efficacy of tenofovir as there is no observed relationship between genotype and response rates for the related nucleotide adefovir (MS section 6.9.2).

In Study 0102[4], there were no statistically significant differences between treatment groups at baseline (section 6.3.2.2). However, the table of baseline characteristics for Study 0103[5] (MS Table 8) appears to be a copy of the same table for Study 0102 (MS Table 7). The ERG therefore checked the baseline characteristics for study 0103 in the CIC Clinical Study Report.

[redacted]

[redacted] Baseline ALT was grouped into two categories in both studies, but the definitions differed between the studies (study 0102[4]: ≤ 2x upper limit of normal (ULN) or > 2 × ULN; study 0103[5]: ≤ 4x ULN or > 4x ULN) (Table 11).

Study 0103[5] excluded patients with ALT levels between 1 and 2 x ULN, but the MS acknowledges that these patients may be considered for treatment in practice. For study 0102,[4] randomisation was stratified on prior lamivudine or emtricitabine exposure and geographic location, but on ALT value and geographic location for study 0103.[4]

The population in both studies was described as nucleoside-naïve, however, the MS states that some participants were "lamivudine and/or emtricitabine pre-treated either as part of the trial protocol" (tenofovir 43/250, adefovir 23/125)[4] "or protocol violations" (tenofovir 8/176, adefovir

1/90).[5] Expert clinical opinion sought by the ERG suggests that these patients are unlikely to have different outcomes from those who were not pre-treated.

Other than the differences described above, the two RCTs were generally similar in terms of design and patient characteristics.

The MS identified five ongoing trials, however three of these are open-label extensions of studies 0102, 0103 and 0106 included in the systematic review.[4,5,15,17-19] References have been given for all of these trials and summary details of the population, comparators, primary endpoint, and main inclusion criteria are tabulated (MS Table 4). As stated earlier, the ERG conducted a search of clinicaltrials.gov, and found one additional ongoing RCT of tenofovir (section 3.1.1.1).

A further 46 non-randomised studies were identified, of which only five were included and used for data on the incidence of drug resistance (MS section 6.8).[20-25] Another study, which was excluded from the systematic review due to the small sample size, was included for assessment of the incidence of drug resistance, as it was one of two studies evaluating tenofovir in patients who failed to respond to adefovir.[25,26] Initially the MS did not report the reasons for the exclusion of the remaining studies or provide a list of references. After seeking clarification from the manufacturer, a bibliography of the 46 non-randomised studies was provided (see Appendix). The ERG has not systematically checked whether these reflect the scope / decision problem. It is noted that some of them include a proportion of patients co-infected with HIV / HBV.

3.1.3 Description and critique of the approach to validity assessment

The MS quality assessed three trials: 0102, 0103 and 0106. The ERG did not check the assessment of study 0106 for reasons stated earlier (see section 3.1.2.1). The manufacturer's quality assessment of the RCTs was appropriate and used the NICE criteria. The ERG quality assessment agrees with the manufacturer's assessment (see Table 2).

The MS also presents a table of critical appraisal of six 'relevant non-RCTs' (MS Table 22) and describes the studies as 'generally of low quality' (MS section 6.8.3). However, the appraisal is limited to a brief statement of methods, number of participants, and publication as abstract or full paper. Established criteria were not applied to studies, and there is no discussion.

Twenty three RCTs (including study 0102 and 0103) were eligible for the MTC. Other than studies 0102 and 0103 they were not quality assessed.

Table 2 Manufacturer and ERG assessment of trial quality

NICE Quality Assessment Criteria for RCTs		
1. How was allocation concealed?		
	Study 0102	Study 0103
MS:	Double-blind	Double-blind
ERG:	Adequate	Adequate
Comment: The MS has confused allocation concealment with blinding of participants, personnel and outcome assessors. However, allocation concealment was adequate so no risk of bias.		
2. Adequacy of randomisation technique		
	Study 0102	Study 0103
MS:	Randomisation was stratified based on prior therapy with LAM or emtricitabine exceeding 12 weeks (yes/no), and by region (North America, Europe, Australia/New Zealand). A centralised randomisation procedure was used in which numbered bottles were assigned to participants via an interactive voice response system (IVRS) according to the randomisation code.	Randomisation was stratified by screening ALT level (≤ 4 and > 4 × ULN) and by region (North America, Europe, and Australia/New Zealand). A centralised randomisation procedure was used in which numbered bottles were assigned to participants via an IVRS according to the randomisation code.
ERG:	Adequate	Adequate
3. Was a justification of the sample size provided?		
	Study 0102	Study 0103
MS:	Yes	Yes
ERG:	Yes	Yes
4. Was follow-up adequate?		

	Study 0102	Study 0103
MS:	Yes	Yes
ERG:	Yes	Yes
5. Were the individuals undertaking the outcomes assessment aware of allocation?		
	Study 0102	Study 0103
MS:	No	No
ERG:	No	No
6. Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.		
	Study 0102	Study 0103
MS:	Parallel	Parallel
ERG:	Parallel	Parallel
Comment:		
7. Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?		
	Study 0102	Study 0103
MS:	RCT was multinational with participating centres from the US (15 sites), Germany (10 sites), Australia (8 sites), France (8 sites), Poland (6 sites), Canada (5 sites), Bulgaria (4 sites), Czech Republic (4 sites), Greece (4 sites), Turkey (4 sites), New Zealand (3 sites), Spain (3 sites), Italy (2 sites), the United Kingdom (2 sites), and the Netherlands (1 site).	RCT was multinational with participating centres from the US (20 sites), Germany (13 sites), Australia (10 sites), France (7 sites), Poland (7 sites), Canada (5 sites), Turkey (5 sites), Bulgaria (4 sites), Czech Republic (4 sites), New Zealand (4 sites), Spain (4 sites), the United Kingdom (3 sites), Greece (2 sites), Italy (1 site), and the Netherlands (1 site).
ERG:	79 sites in 15 countries, 2 UK sites.	90 sites in 15 countries, 3 UK sites
Comment: The MS does not comment whether clinical practice in the other countries is likely to differ from UK practice. Expert opinion suggests that clinical practice in these countries is similar to the UK, although treatment may be started earlier in the US.		
8. How do those included in the RCT compare with patients who are likely to receive		

the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.		
	Study 0102	Study 0103
MS:	Comparable to patients in the UK who have HBeAg-negative CHB. Given that UK patients often originate from countries outside of the UK the multinational design of the study provides a representative population.	Comparable to patients in the UK who have HBeAg-positive CHB. Given that UK patients often originate from countries outside of the UK the multinational design of the study provides a representative population.
ERG:	Comparable	Comparable. However, section 6.9.2 notes that trial 0103 excluded patients who had ALT levels between 1 and 2 times the ULN, who may be considered for treatment in practice.
9. Were the study groups comparable?		
	Study 0102	Study 0103
MS:	Yes	Yes
ERG:	Yes	[redacted]
10. Were the statistical analyses used appropriate?		
	Study 0102	Study 0103
MS:	Yes	Yes
ERG:	Yes	Yes
11. Was an intention-to-treat analysis undertaken?		
	Study 0102	Study 0103
MS:	Yes	Yes
ERG:	“Randomised and treated” (received at least one dose of treatment)	“Randomised and treated” (received at least one dose of treatment)
12. Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?		
	Study 0102	Study 0103

MS:	No	No
ERG:	No	No
13. For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?		
	Study 0102	Study 0103
MS:	The doses of TDF and ADV dipivoxil were according to the SPC.	The doses of TDF and ADV dipivoxil were according to the SPC.
ERG:	Yes	Yes

3.1.4 Description and critique of manufacturer's outcome selection

The outcomes selected by the manufacturer are appropriate and match the NICE scope/decision problem. The primary outcome in the two RCTs (0102[4] and 0103[5]) is a composite endpoint defined as histologic response and HBV DNA below 400 copies/mL (histologic response is defined as a ≥2-point reduction in Knodell necroinflammatory score without worsening of fibrosis) at 48 months. These constituent outcomes are also reported separately. Expert clinical opinion suggests that liver histology is not considered an appropriate primary outcome measure, as liver biopsy results at one or two years are unlikely to show much change, and are subject to sampling error and a lack of inter- and intra-rater reliability. The primary outcome measures used in the MTC were HBV DNA <300 copies/mL and HBeAg seroconversion, which are accepted measures of treatment effectiveness.

The secondary outcomes in the two RCTs were liver histology (proportion with improvement in necroinflammation, proportion with worsening in fibrosis, mean change from baseline in Knodell and Ishak necroinflammatory score, and fibrosis score) with limitations as noted above, alanine aminotransferase response (proportion with normal ALT and normalised ALT, mean change from baseline), serology (proportion with HBsAg loss and seroconversion; proportion with HBeAg loss and seroconversion), and resistance. There do not appear to be any other outcomes in the trials that are not reported in the MS. Adverse events are adequately reported.

Although time to treatment failure, survival, and health related quality of life were included as outcomes in the decision problem they were not reported by the included RCTs.

3.1.5 Description and critique of the manufacturer's approach to trial statistics

The MS states that study 0102[4] and 0103[5] stratified a two-sided 95% confidence interval (CI) (stratified by baseline ALT ≤ 2 × ULN or > 2 × ULN or baseline ALT ≤4x ULN or >4x ULN, Table 11) to evaluate differences in the proportion of complete responders between treatment groups. The MS states that the CI was not stratified for the randomisation strata (geographic region or prior lamivudine or emtricitabine experience), with the difference calculated as tenofovir 300 mg o.d. minus adefovir 10 mg o.d. for each stratum. It is unclear how valid and relevant this method is. The MS includes results for what appear to be post-hoc subgroup analyses, but there is no certainty that the studies were adequately powered for this type of analysis.

The manufacturer performed a "randomised-and-treated" (RAT) analysis based on all patients who had been randomised and had received at least one dose of study medication. Missing data were treated as "treatment failures" for the RAT analysis. This seems a reasonable approach.

The majority of outcome measurements were binary, reported as proportion of patients (numbers and percentage). CIs and p values were reported for some outcomes only. Outcomes for HBeAg positive and negative patients were reported separately. The MS stated that no adjustments for multiple comparisons were required (MS Table 11), as there was a single primary endpoint to be compared between two treatment groups.

The MS notes that no interim analysis was performed prior to week 48 and none is presented in the report (MS Table 11).

3.1.6 Description and critique of the manufacturer's approach to the evidence synthesis

A narrative review of studies 0102[4], 0103[5] and 0106[15] is provided (study 0106 not discussed here for reasons given earlier). The tabulated data reflects data in the trials, although there are slight inconsistencies between the trial summary of 0102[4] (MS section 6.4.1) and Figure 2 in the MS. However, these discrepancies are minor and should not affect the bottom line results. The results of six non-RCTs are also tabulated (MS section 6.8). A meta-analysis of the two trials (0102[4] and 0103[5]) is not provided, however this is appropriate as they are different patient groups (HBeAg positive HBeAg negative).

Mixed Treatment Comparison (MTC)

As mentioned, the manufacturer report a Bayesian MTC (also sometimes referred to as the meta-analysis in the MS). The rationale for doing the MTC was because no RCTs were identified that directly compared tenofovir with nucleos(t)ides other than adefovir (e.g. lamivudine, telbivudine, entecavir). A summary of the methodology was given in the MS (MS section 6.6.1). Further details are provided in AIC Appendix 4.

The ERG appraised the methodological quality of the MTC (Table 3).

Table 3 ERG appraisal of the MTC

Appraisal criteria	**Criteria met**
A. CONCEPTUAL BASIS	
1. Is a justification given for conducting an MTC?	Yes
B. SYSTEMATIC PROCESSES	
2. Is a comprehensive and transparent search strategy reported?	Partial See section 3.1.1.1 for details
3. Are inclusion / exclusion criteria adequately reported?	Yes
4. Is the number of included /excluded studies from the MTC reported, with reasons for exclusions?	Yes
5. Is a visual representation of the data networks provided?	Yes
6. Are the data from included studies extracted and tabulated?	Partial Limited methodological details and baseline characteristics are presented for the RCTs of nucleos(t)ide naïve patients only, not for LAM refractory patients. Outcome data for all RCTs are presented.
7. Is the quality of the included studies assessed?	No (other than trials 0102 and 0103)
C. STATISTICAL ANALYSIS	
8. Are the statistical procedures adequately described	Yes

and executed?	
9. Is there a sufficient discussion of heterogeneity?	Partial
10. Is the type of model used (i.e. fixed or random effects) reported and justified?	Yes
11. Was sensitivity analysis conducted?	Yes
12. Is any of the programming code used in the statistical programme provided (for potential verification?)	No
D. PRESENTATION AND INTERPRETATION OF THE EVIDENCE	
13. Is there a tabulation/ illustration of results for each intervention and for each outcome?	Yes
14. Is there a narrative commentary on the results?	Yes
15. Does the discussion of the results reflect the data presented?	Yes
16. Have the authors commented on how their results compare with other published studies (e.g. MTCs), and offer any explanation for discrepancies?	No
17. Have the authors discussed whether or not there are any differences in effects between the direct and indirect evidence?	No (although data are presented in MS Appendix 4, Table 6 which allows a comparison to be made)

Most of the criteria were met indicating a reasonable approach. However, there were instances when the criteria were partially met or not met. For example, search strategies were current to August 2007, and any new RCTs published since then will not have been included (although as explained in section 3.1.1.1, the ERG has not identified any new tenofovir RCTs based on an update search of PubMed).

As limited methodological details and baseline characteristics are presented, the ERG is unable to ascertain how similar the trials are to each other in terms of:

- Patient characteristics e.g. age, sex, race/ethnicity, presence of co-morbidities and co-infections, (other than HIV), stage and grade of liver disease (e.g. the proportion who were cirrhotic)
- Study location (e.g. country/countries)

- Dose / regimen of the drugs
- The time period that the trials were done (although can estimate this from looking at publication dates).

The MS does not make any statement regarding the similarity of the studies in terms of these factors. This limitation should be kept in mind in the interpretation of the results.

There is limited discussion of heterogeneity. As stated earlier, the MS reports that the inclusion criteria for the MTC were more "stringent" than for the wider systematic review "to ensure only comparable studies were combined statistically" (MS section 6.6). For HBeAg-positive treatment naïve patients, the analysis was conducted using a random-effects model as significant heterogeneity was identified.

[redacted] Heterogeneity between RCTs for other subgroups was not discussed, other than to state a random-effects model was used. [redacted]

It was noted by the ERG that the HBeAg seroconversion / loss rates entered into the MTC for one of the studies (adefovir + lamivudine versus lamivudine + placebo in HBeAg-positive nucleoside naïve patients)[13] were based on conference abstract now superseded by a full publication (NB. The trial was fully published in February 2008, but was not identified by the MS's literature search which was conducted in August 2007). There is a discrepancy between the data reported in the full publication and the abstract.

[redacted]

Table 4 Data discrepancies between abstract and full publication of HBeAg seroconversion and loss rates

It should be noted that the ERG has not conducted a systematic check of all the data entered into the MTC by the manufacturer.

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In summary, the ERG considers that the MTC reported in the MS is generally reasonable, notwithstanding the potential limitations discussed above. However, it must be borne in mind that it was only possible to conduct an MTC for the HBeAg positive treatment naïve subgroup. The clinical-effectiveness of tenofovir versus the other nucleos(t)ides for the other patient subgroups is not clear.

3.2 Summary statement of manufacturer's approach

The submitted evidence generally reflects the decision problem defined in the MS. Relatively brief information is provided by the MS on the process of identification and selection of studies, making it difficult to potentially reproduce their systematic review. No details about the methods employed for quality assessment of the included RCTs are provided. As the methods employed for the quality assessment of the included RCTs are unknown, the risk of bias is uncertain.

Table 5 Quality assessment (CRD criteria) of manufacturer's review

CRD Quality Item: Yes/ No/ Partially / Uncertain (with comments)

1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	1. Yes, but there is only a summary is in the MS, with the main inclusion criteria an appendix. However, the review question is only addressed in relation to TDF and ADV, although other comparators are included in the scope.
2. Is there evidence of a substantial effort to search for all relevant research? Are all studies identified?	2. Partial - overall search strategies were adequate, but not exhaustive or clear.
3. Is the validity of included studies adequately assessed?	3. Only studies 0102 and 0103 are adequately assessed, no assessment of the MTC studies.
4. Is sufficient detail of the individual studies presented?	4. Partial, the baseline characteristics for study are 0103 missing and the table provided is a duplicate of study 0102.
5. Are the primary studies summarised appropriately?	5. Yes, the MS reports a narrative synthesis of studies 0102, 0103 and an MTC.

3.3 Summary of submitted evidence

The results of the two RCTs of tenofovir versus adefovir (studies 0102 and 0103) are summarised in sections 3.3.1 to 3.3.8 by outcome measure. The results of the MTC comparing tenofovir with other nucleos(t)ides are then summarised in section 3.3.9.

As mentioned in section 3.1.2, a journal article based on study 0102 and 0103 has now been published.[16] The ERG cross-checked the results of the journal article with those reported in the MS and found a few minor discrepancies. However, none of these alter the overall conclusions of the MS.

3.3.1 Complete response at week 48 (primary outcome)

Tenofovir was significantly more effective than adefovir for both HBeAg-negative and HBeAg-positive patients in terms of the primary outcome: the proportion of patients with a complete response at 48 weeks (Table 6). This is a composite endpoint defined as histologic response and HBV DNA below 400 copies/mL, and whilst a significant difference was found in the

proportion of patients with HBV DNA below 400 copies/mL, there was no significant difference in histologic response (Table 7).

Table 6 Complete response[‡] at week 48

Study & patients	Response category (n, %)	TDF	ADV	Difference estimate (95% CI)[†]	P-value
Study 0102[4]		**N=250**	**N=125**		
HBeAg-negative	Yes	177 (70.8)	61 (48.8)	23.5% (13.2, 33.8)	<0.001
	No	73 (29.2)	64 (51.2)		
Study 0103[5]		**N=176**	**N=90**		
HBeAg-positive	Yes	117 (66.5%)	11 (12.2%)	54.1% (44.6, 63.6)	<0.001
	No	59 (33.5%)	79 (87.8%)		

[†]Difference and CI are adjusted for baseline ALT stratum.

[‡]Complete response is a composite endpoint defined as histologic response and HBV DNA below 400 copies/mL.

Table 7 Histologic response[§] at week 48

Study & patients	Response category (n, %)	TDF	ADV	Difference estimate (95% CI)[†]	P-value
Study 0102[4]		**N=250**	**N=125**		
HBeAg-negative	Yes	181 (72.4)	86 (68.8)	5.2% (-4.5, 14.9)	0.293
	No	69 (27.6)	39 (31.2)		
Study 0103[5]		**N=176**	**N=90**		
HBeAg-positive	Yes	131 (74.4%)	61 (67.8%)	5.8% (-5.6, 17.2)	0.320
	No	45 (25.6%)	29 (32.2%)		

[†]Difference and CI are adjusted for baseline ALT stratum.

[§] Histological response/improvement was defined as a ≥2-point reduction in Knodell necroinflammatory score without worsening in fibrosis.

3.3.2 HBV DNA

In both studies, significantly more patients receiving tenofovir had reductions in HBV DNA levels below 400 (Table 8), 300 and 169 copies/mL (Table 9) at week 48 than with adefovir (p<0.001), and the mean reduction from baseline in plasma HBV DNA was significantly greater with tenofovir than adefovir (p<0.001). (Table 10)

Table 8 HBV DNA <400 copies/mL at week 48

Study & patients	Response category (n, %)	TDF	ADV	Difference estimate (95% CI)[†]	P-value
Study 0102[4]		**N=250**	**N=125**		
HBeAg-negative	Yes	236 (94.4)	80 (64.0)	30.3% (21.6, 39.1)	<0.001
	No	8 (3.2)	41 (32.8)		
	Missing	6 (2.4)	4 (3.2)		
Study 0103[5]		**N=176**	**N=90**		
HBeAg-positive	Yes	140 (79.5%)	12 (13.3%)	65.9% (56.8, 75.0)	<0.001
	No	29 (16.5%)	74 (82.2%)		
	Missing	7 (4.0%)	4 (4.4%)		

[†]Difference and CI are adjusted for baseline ALT stratum.

Table 9 Proportion with HBV DNA below different thresholds at week 48

Study & patients	Response category (n, %)	TDF	ADV	Difference estimate (95% CI)	P-value
		N=250	**N=125**		

Study 0102[4]	<300 copies/mL	230 (92.0)	74 (59.2)	NR	P<0.001
HBeAg-negative	<169 copies/mL	228 (91.2)	70 (56.0)	NR	P<0.001
		N=176	**N=90**		
Study 0103[5]	<300 copies/mL	130 (74)	11 (12)	NR	P<0.001
HBeAg-positive	<169 copies/mL	121 (69)	8 (9)	NR	P<0.001

NR: not reported.

Table 10 Mean (SD) reduction from baseline in plasma HBV DNA at week 48

Study & patients	**TDF**	**ADV**	**p-value**
Study 0102[4] HBeAg-negative	-4.57 log_{10} copies/mL (1.347)	-4.07 log_{10} copies/mL (1.331)	P<0.001
Study 0103[5] HBeAg-positive	-6.17 log_{10} copies/mL (1.067)	-3.93 log_{10} copies/mL (1.738)	p<0.001

3.3.3 Histology

There were no significant differences in histology between tenofovir and adefovir at 48 weeks in either study (Table 11).

Table 11 Histology outcomes at week 48

	TDF	**ADV**	**Difference estimate (95% CI)**	**P-value**
Study 0102, HBeAg-negative[4]	**N=250**	**N=125**		
Proportion with improvement in	194 (77.6)	93 (74.4)	5.1% (-3.9, 14.1)	P=0.268

necroinflammation (Knodell), n (%)				
Proportion with worsening in fibrosis (Knodell), n (%)	16 (6.4)	11 (8.8)	-0.2% (-5.4, 5.1)	P=0.955
Mean change from baseline in Knodell necroinflammatory score (SD)	-3.5 (2.5)	-3.4 (2.36)	-0.11 (-0.65, 0.43)	p=0.693
Mean change from baseline in Knodell fibrosis score (SD)	-0.1 (0.86)	-0.1 (0.88)	-0.03 (-0.23, 0.17)	P=0.750
Mean change from baseline in Ishak necroinflammatory score (SD)	-2.6 (1.93)	-2.6 (1.90)	-0.01 (-0.44, 0.42)	P=0.964
Mean change from baseline in Ishak fibrosis score (SD)	-0.2 (0.92)	-0.2 (1.07)	0.01 (-0.22, 0.24)	P=0.947
Study 0103, HBeAg-positive[5]	**N=176**	**N=90**		
Proportion with improvement in necroinflammation (Knodell), n (%)	137 (77.8)	64 (71.1)	6.2% (-4.8, 17.3)	NR
Proportion with worsening in fibrosis (Knodell), n (%)	3 (1.7)	3 (3.3)	-1.7 (-5.9, 2.1)	NR
Mean change from baseline in Knodell necroinflammatory score (SD)	-3.6 (2.30)	-3.2 (2.35)	-0.34 (-0.98, 0.30)	NR
Mean change from baseline in Knodell fibrosis score (SD)	-0.1 (0.61)	-0.2 (0.79)	0.04 (-0.16, 0.24)	NR
Mean Knodell necroinflammatory score (SD)	4.7 (2.02)	5.2 (1.96)	NR	P=ns
Mean change from baseline in Ishak necroinflammatory score (SD)	-2.7 (1.70)	-2.6 (1.94)	-0.01 (-0.51, 0.48)	NR
Mean change from baseline in Ishak fibrosis score (SD)	-0.2 (0.69)	-0.1 (0.85)	-0.07 (-0.28, 0.15)	NR

NR: not reported; p=ns: not statistically significant.

3.3.4 Alanine aminotransferase (ALT) response

In study 0102, a higher mean baseline level of ALT in patients receiving adefovir led to a greater mean change from baseline in this group. There was no significant difference in the proportion of patients with normalised ALT at 48 weeks (Table 12).

In study 0103, significantly more patients receiving tenofovir than adefovir had normalised (p=0.032) or normal (p=0.018) ALT at 48 weeks (Table 12).

Table 12 Alanine aminotransferase levels at week 48

	TDF	**ADV**	**Difference estimate (95% CI)**	**P-value**
Study 0102[4], HBeAg-negative	**N=250**	**N=125**		
Baseline ALT, U/L, mean (SD)	127.5 (101.21)	163.6 (146.02)	NR	NR
Change from baseline, U/L, mean (SD)	-95.0 (102.31)	-124.4 (137.23)	NR	P=0.040
Proportion with normalised ALT, n (%)	180/236 (76)	91/118 (77)	NR	P=ns
Proportion with normal ALT, n (%)	193/250 (77)	97/125 (78)	NR	NR
Study 0103[5], HBeAg-positive	**N=176**	**N=90**		
Proportion with normalised ALT, n (%)	115/176	49/90	13.6% (1.1, 26.1)	P=0.032
Proportion with normal ALT, n (%)	122/176	49/90	14.9 % (2.5, 27.2)	P=0.018

NR: not reported; p=ns: not statistically significant.

3.3.5 Serology

In study 0102 (HBeAg-negative patients), no participants in either treatment group experienced HBsAg loss or seroconverted to anti-HBs by week 48.

In study 0103 (HBeAg-positive patients), a similar proportion of evaluable participants (note denominators in Table 13 below) receiving tenofovir or adefovir achieved HBeAg loss and

HBeAg seroconversion. Significantly more tenofovir patients than adefovir patients achieved HBsAg loss at 48 weeks (p=0.018).

Table 13 Serology in Study 0103 (HBeAg-positive) at week 48

	TDF	**ADV**	**Difference estimate (95% CI)**	**P-value**
Achieved HBeAg loss at week 48, n (%)	34/153 (22)	14/80 (18)	NR	NR
Achieved HBeAg seroconversion, n (%)	32/153 (21)	14/80 (18)	NR	NR
Achieved HBsAg loss at week 48, n (%)	5/158 (3)	0/82 (0)	NR	P=0.018
Achieved HBsAg seroconversion, n (%)	2/158 (1)	0/82 (0)	NR	NR

NR: not reported.

3.3.6 Resistance

In study 0102 (HBeAg-negative) of 50 serum isolates from viraemic participants, eight (3.2%) were in the tenofovir group compared with 42 (33.6%) receiving adefovir. Seven viraemic participants in the adefovir group (compared with none receiving tenofovir) developed changes at conserved site residues within the HBV polymerase after 48 weeks. No participant developed a substitution in the HBV polymerase/reverse transcriptase associated with resistance to tenofovir.

In study 0103 (HBeAg-positive), among the serum isolates from viraemic participants, 31 (17.6%) were from the tenofovir group, while 75 (83.3%) received adefovir. At 48 weeks, 2 viraemic participants receiving tenofovir, and 8 viraemic participants receiving adefovir had conserved-site changes. No participant developed a substitution in the HBV polymerase/reverse transcriptase associated with resistance to tenofovir.

Pooled analysis of tenofovir resistance data

The MS presents pooled analysis of the virologic resistance to tenofovir, [redacted]

The MS states that the findings demonstrate that the incidence of virologic resistance to tenofovir 'cannot be higher than 0.23% (1/423) in the first year of treatment in naïve patients, or more than 0.82% (1/122) in lamivudine resistant patients' (MS Section 6.10.1.5). However, there seems to be some discrepancy between the denominator reported in the text for treatment naïve patients (n=424) and that reported in MS Table 25 (n=577). These data are discussed further in section 4.3.2.2.

3.3.7 Open-label extension phase weeks 48-96

At week 48 of the RCTs, patients were given the option to continue or initiate treatment with tenofovir (remaining blinded to their original treatment assignment). Patients with HBV DNA ≥ 400 copies /mL at week 72 were eligible to be switched to open-label emtricitabine/tenofovir combination treatment. Data from this ongoing phase were not tabulated in the MS, simply summarised in a list of statements. In addition, the data are observational and unpublished, therefore should be interpreted with caution.

Study 0102 (HBeAg negative): Three hundred and forty seven patients (235/250 and 112/125 participants originally randomised to tenofovir and adefovir, respectively) entered the open-label phase, of which 95.7% and 98.2%, respectively, completed the study through to week 96

Key results reported in the MS include:

- At week 96, a similar proportion of participants in the tenofovir–tenofovir group (90.6%) and in the adefovir–tenofovir group (89.3%) had an HBV DNA value < 400 copies/mL (Long-term evaluation (LET) analysis, including patients who switched to tenofovir/emtricitabine).
    - No amino acid substitutions at conserved sites within the HBV DNA polymerase were detected.
    - 96 weeks of continued or 48 weeks of deferred treatment with tenofovir did not produce HBsAg loss or seroconversion.

Study 0103 (HBeAg positive): Two hundred and thirty eight patients (154/176 and 84/90 participants originally randomised to tenofovir and adefovir, respectively) entered the open-label phase, of which 94.2% and 98.8%, respectively, completed the study through to week 96.

Key results reported in the MS include:

- Sixteen participants in the tenofovir–tenofovir group and 13 participants in the adefovir-tenofovir group switched to open-label emtricitabine/tenofovir during the open-label period due to confirmed viraemia. Twenty-three of these participants did not achieve viral suppression < 400 copies/mL up to Week 96.

- At week 96, a similar proportion of participants in the tenofovir–tenofovir group (77.6%) and in the adefovir–tenofovir group (77.9%) had an HBV DNA value < 400 copies/mL (LTE analysis, including patients who switched to tenofovir+emtricitabine).

- The proportion of participants achieving HBeAg loss or HBeAg seroconversion (HBeAg loss plus positive anti-HBe result) increased by 11% at week 96 in those switching from adefovir to tenofovir, and increased slightly in the group receiving continued tenofovir therapy.

- The development of conserved site changes in HBV DNA polymerase was infrequent and did not correspond with virologic breakthrough among participants treated with up to 96 weeks of tenofovir.

3.3.8 Summary of results: subgroup analysis

The MS presents subgroup analyses for cirrhotic patients and lamivudine experienced patients in studies 0102 and 0103 combined. Both analyses were published as conference presentations, but did not appear in the CIC clinical study reports. As such, they appear to be post-hoc analyses and should be interpreted with caution.

Cirrhotic patients (n=123) 59% HBeAg-negative
The MS states that the results for cirrhotic patients (HBV DNA < 400 copies/mL: tenofovir 85%, adefovir 48%, p<0.001) were similar to those for the total trial population [376/426 (88.3%) participants receiving tenofovir had HBV DNA below 400 copies/mL at 48 weeks].

Lamivudine experienced patients (n=70), 87% HBeAg-negative
The MS states that tenofovir was found to be as effective in this population as in the total trial population (HBV DNA < 400 copies/mL in patients with tenofovir: 88% lamivudine experienced,

86% lamivudine naïve, p value not reported). A comparison of tenofovir versus adefovir was not reported in this subgroup.

3.3.9 Summary of results for the MTC

The MTC was conducted for two outcomes: the probability of HBeAg seroconversion, and the probability of achieving HBV DNA <300 copies /mL. Four subgroups were considered:

1. HBeAg-positive nucleos(t)ide naïve patients (n=13 RCTs)
2. HBeAg-negative nucleos(t)ide naïve patients (n= 4 RCTs)
3. HBeAg-positive lamivudine refractory patients (with and without HIV co-infection) (n=5 RCTs)
4. HBeAg-negative lamivudine refractory patients (n=1 RCT)

1. HBeAg-positive nucleos(t)ide naïve participants

[redacted] The probability of achieving undetectable HBV DNA with tenofovir was found to be significantly higher than that for all other treatments considered in the analysis at the 0.05 level, including entecavir and telbivudine. The analysis demonstrated that there is a 98% probability that tenofovir is the most potent nucleos(t)ide considered in this analysis in terms of this outcome.

All treatments were associated with a significantly higher chance of achieving undetectable HBV DNA than placebo. Tenofovir, entecavir and telbivudine were also found to be significantly superior to lamivudine at the 0.05 level. See Table 14 for 'key results'.

All treatments other than telbivudine +lamivudine in combination were found to significantly increase the probability of HBeAg seroconversion at one year relative to placebo at the 0.05 level. However, this analysis identified no statistically significant differences between nucleos(t)ides for this outcome. One of the trials included in the analysis of seroconversion includes patients co-infected with Hepatitis D, which is outside the scope of the appraisal. As mentioned earlier (section 3.1.6), this is a small trial and probably does not have much impact on the overall result.

Table 14 Key results of the MTC after 1 year of treatment

Treatment (No. of trials in analysis)	% pts HBV DNA <300 copies/mL (95% CrI)	OR vs LAM (95% CrI)	% pts HBeAg Seroconverted (95% CrI)	OR vs LAM (95% CrI)
TDF (1)	93.7% (80.0%, 99.3%)[l,p,*]	52.78 (6.427, 226.4)	26.7% (11.1%, 49.1%)[p]	1.275 (0.441, 2.984)
ETV (3)	73.1% (57.6%, 87.6%)[l,p]	4.941 (2.228, 11.6)	23.9% (15.7%, 33.9%)[p]	1.027 (0.758, 1.361)
TEL (3)	62.9% (44.8%, 81.7%)[l,p]	3.091 (1.275, 7.517)	25.7% (17.1%, 36.1%)[p]	1.132 (0.827, 1.51)
TEL + LAM (1[†])	53.3% (21.9%, 84.3%)[p]	2.576 (0.434, 9.292)	13.5% (4.2%, 29.3%)	0.532 (0.15, 1.289)
ADV (4)	48.8% (25.8%, 77.5%)[p]	1.861 (0.551, 5.715)	22.1% (11.6%, 36.1%)[p]	0.946 (0.467, 1.703)
LAM (9[‡])	38.4% (33.9%, 42.8%)[p]	-	23.5% (16.4%, 32.1%)[p]	-
ADV + LAM (1[†])	37.5% (12.5%, 68.7%)[p]	1.182 (0.231, 3.651)	28.1% (13.2%, 47.6%)[p]	1.344 (0.536, 2.814)
Placebo (5[‡])	7.1% (1.5%, 18.5%)	0.129 (0.025, 0.373)	10.7% (5.6%, 17.7%)	0.393 (0.213, 0.65)

CrI, credible (Bayesian probability) interval; OR, odds ratio showing how many times higher probability of this outcome is with the treatment in question, compared with lamivudine.
[*] Significantly superior to all 7 treatments included in the analysis at the 0.05 level.
[l] Significantly superior to lamivudine at the 0.05 level.
[p] Significantly superior to placebo at the 0.05 level.
[†] n<60.
[‡] Data on patient achieving undetectable HBV DNA by PCR were unavailable for 3 placebo-controlled lamivudine trials, therefore 6 lamivudine trials and 2 placebo trials were used in the analysis.

It should be noted that the analyses are based on a small number of trials. For some of the drugs, including tenofovir, there is only one trial; therefore the results of the MTC are largely dependent upon the strengths and weaknesses of these individual trials. Quality assessment was undertaken by the manufacturer for the tenofovir trial only, so the quality of the remaining trials is unknown. The results are therefore subject to some degree of uncertainty.

2. HBeAg-negative nucleos(t)ide naïve patients

Four RCTs were included but did not form a connective network. A fifth study (2 year data, did not meet inclusion criteria) was included in a sensitivity analysis but meaningful data could not be generated on this subgroup alone. An additional analysis combining trials on HBeAg-positive

and HBeAg-negative patients in which the proportion of patients who were HBeAg-positive was considered as a covariate produced similar results to the HBeAg-positive subgroup.

3. HBeAg-positive lamivudine refractory patients

No trials of tenofovir in HBV mono-infected lamivudine refractory patients were identified, (although this is not explicit in section 6.6.2 of the MS) and therefore an MTC including tenofovir was not reported. A sensitivity analysis was conducted in which two trials of HIV/HBV co-infected patients were considered alongside those on HBV mono-infected patients, but the ERG has not included this as it is outside the scope of the appraisal.

The conclusion that tenofovir was significantly superior to all other nucleos(t)ides for achieving undetectable HBV DNA (<300 copies/mL) in MS section 6.6.3 is misleading as it does not make it explicit that this is based on a qualitative sensitivity analysis which included some trials of HBV/HIV co-infected patients.

4. HBeAg-negative lamivudine refractory patients

Only one RCT met the inclusion criteria therefore an MTC could not be conducted.

3.3.10 Non-RCT evidence

Evidence from six low quality non-randomised studies is used by the MS to provide additional evidence on the safety and efficacy of tenofovir in situations that have not been evaluated in RCTs (MS section 6.8). Five of these studies were selected from a total of 46 non-randomised studies meeting the inclusion criteria for the systematic review. However, the selection criteria are not defined; the MS simply states that the five studies "related to the use of tenofovir in HBV mono-infected patients" and "were used to provide data on the incidence of drug resistance". An additional study that did not meet the inclusion criteria for the systematic review on grounds of size was also presented. Given this lack of clarity, and the methodological concerns of the studies, the ERG urges caution in the interpretation of their results.

Summary points in the MS include:

- Studies suggest that tenofovir is also an extremely effective treatment in patients who are lamivudine resistant and in those who have both lamivudine resistance and have failed adefovir.

- There is evidence of continued efficacy and safety in up to five years of continuous treatment. (Note these data are not tabulated in the MS).
- No studies identified any cases of virologic resistance to tenofovir.

The MS states that these findings must be interpreted cautiously due to the methodological weakness of these studies.

3.3.11 Summary of adverse events

Adverse events up to week 48

The MS provides a safety overview of tenofovir RCTs, with relevant incidence rates of common adverse events (MS Table 17 and 18), but statistical comparisons are not always reported. Both of the included studies performed a RAT analysis on the safety data (all randomised participants who had at least one dose of study medication).[4,5] The MS reports that across both studies, the most common adverse events were headache, nasopharyngitis, back pain, nausea, fatigue and abdominal pain. However, statistically significantly more participants did have at least one treatment related adverse event in the tenofovir treatment group in study 0103 ($p = 0.018$).[5] The MS attributes this to a higher incidence of mild nausea in the tenofovir treatment group (tenofovir 13.6% vs 1.1%, $p < 0.001$). Incidence of grade three to four adverse events, as well as serious adverse events were reported to be similar between treatment groups, with no reported deaths in either study.

Study 0102[4]: Incidence of arthralgia was statistically significantly higher for the tenofovir treatment group (tenofovir 6% vs adefovir 0%; $p = 0.003$), but this was the only adverse event that was statistically significant between the treatment groups. However, only those adverse events occurring in at least 5% of participants in either treatment group were reported. Treatment-related adverse events classed as 'investigations' were statistically significantly higher in the adefovir than tenofovir group (5.2% vs 7.6 % respectively; $p = 0.029$) and the MS attributes this to an increased incidence of blood creatine phosphokinase adverse events (4% vs 0.4% respectively) and blood creatine increased adverse events (3.2% vs 0.4% respectively).

Study 0103[5]: Gastrointestinal disorders were statistically significantly more frequent in the tenofovir treatment group ($p = 0.011$) and this is attributed by the MS to the increased incidence of nausea. There were no statistically significant differences between treatment groups in

hepatobiliary disorders. However, only adverse events occurring in at least 5% of participants in either treatment group were reported. Reproductive system and breast disorders only occurred in the tenofovir treatment group (tenofovir 5.1% vs ADF 0%, p=0.031), although the MS states that these were not related to study drug. The MS only presents the total number of patients for grade 2, 3 or 4 adverse events combined. A summary of adverse events from the two studies is provided in Table 15.

Table 15 Key results of adverse events up to week 48

GS-US-174-0102[4]	**TDF N=250**	**ADF N=125**	**P value**
Any AEs, % (n)	70.4 (176)	73.6 (92)	0.546
Incidence of study drug-related AEs, % (n)	16.8 (42)	19.2 (24)	
Grade 3/4 AEs, % (n)	8.8 (22)	8.8 (11)	
Serious AEs, % (n)	4.8 (12)	5.6 (7)	
Discontinuation due to AEs, % (n)	2 (5)	1.6 (2)	
Change of dose/interruption due to AEs, % (n)	1.6 (4)	0.8 (1)	
Death, % (n)	0	0	
GS-US-174-0103[5]	**TDF N=176**	**ADFN=90**	**P value**
Any AEs, % (n)	80.1 (141)	73.3 (66)	0.216
Incidence of study drug-related AEs, % (n)	30.7 (54)	16.7 (15)	0.018
Grade 2, 3 or 4 AEs, % (n)	31.3 (55)	32.3 (29)	0.890
Serious AEs, % (n)	8.5 (15)	7.8 (7)	
Study drug-related serious AEs, % (n)	3.4 (176)	4.4 (90)	
Discontinuation due to AEs, % (n)	0	1.1 (1)	
Death, % (n)	0	0	

There were no statistically significant differences in the frequency of overall incidence of adverse events between tenofovir and adefovir in either study.

Adverse events week 48 – 96 (open-label phase)

After week 48 in studies 0102 and 0103, participants in both groups were able to continue/initiate treatment with open-label tenofovir. While around 95% (Study 0102: n=125; Study 0103: n=145) of participants in the tenofovir and over 98% (Study 0102: n=110; Study 0103: n=83) of participants in the adefovir treatment arm in both RCTs completed 96 weeks of treatment, it is unclear whether the figures in Table 16 are based on these numbers. The most common adverse events remained similar: nasopharyngitis, headache, hypertension, abdominal pain upper, influenza and cough. The MS reports that no interruption or termination of treatment due to common adverse events was required.

Table 16 Key results of adverse events week 48 - 96

GS-US-174-0102[4]	**TDF-TDF**	**ADV-TDF**
Frequency of SAEs, %	4.7	8.9
Discontinuation, n	3 (2 due to fatigue)	0
Death*, n	2	0
GS-US-174-0102[5]	**TDF-TDF**	**ADV-TDF**
Frequency of SAEs, n	Group unknown: 1 facial spasm ; ADV-TDF: 2 (both ALT increases)**	
Discontinuation	1 (AE of serum creatinine increase)	0
Death, n	0	0

*not related to drug treatment

** frequency of SAEs was reported to be similar for both groups

Study 0102:[4] one study-drug related SAE of mild renal impairment was managed with a dose reduction; however it is unclear in which treatment group this event occurred.

Study 0103:[5] the occurrence of on-treatment hepatic flares was slightly higher in the adefovir-tenofovir treatment group than the tenofovir-tenofovir treatment group (adefovir-tenofovir: n=3; tenofovir-tenofovir: n=1) and are reported to be associated with enhanced viral clearance in the adefovir-tenofovir group, compared to an increase in viral load in the tenofovir-tenofovir group. The MS speculates that the increase in viral load may have been caused by poor compliance. One of the participants in the adefovir-TDF treatment group was reported to have lost HBsAg and seroconverted to anti-HBs and anti-HBe. All flares are reported to have either improved or

been resolved by the last assessment, without any suffering from decompensation or associated symptoms.

The MS reports that the safety profile in the open-label extension of tenofovir for both studies is consistent and well tolerated, with no evidence of renal failure, severe renal impairment, renal toxicity or bone events due to the drug treatment.

3.3.12 Summary of Health related quality of life

Health related quality of life was not reported as an outcome in Studies 0102 or 0103.

3.4 Summary

The manufacturer has provided a reasonably unbiased estimate of the treatment effect for tenofovir. The strongest evidence is from the head to head RCTs of tenofovir compared to adefovir in nucleos(t)ide naïve patients at one year. The clinical-effectiveness of tenofovir compared to other nucleos(t)ides is estimated from direct and indirect evidence in an MTC. Whilst this appears generally sound there are limitations around the adequacy of the search for eligible RCTs, the likely similarity of these trials, and the paucity of data for some of the patient subgroups.

The manufacturers interpretation of the clinical evidence (MS section 6.9.1), states that tenofovir has proven potency against HBV, including lamivudine-resistant viral strains. The two trials of tenofovir in HBeAg-positive patients were in HIV co-infected patients. The only evidence there is for the effectiveness of tenofovir in lamivudine resistant patients comes from non-randomised studies, so caution is advised in this interpretation.

4 ECONOMIC EVALUATION

4.1 Overview of manufacturer's economic evaluation

The manufacturer's submission to NICE includes:

i) a review of published economic evaluations relating to the use of nucleos(t)ides in the treatment of CHB (discussed further in section 4.1.1).

ii) a report of an economic evaluation undertaken for the NICE STA process. The cost-effectiveness of tenofovir as a first line treatment, compared with lamivudine, entecavir and adefovir is estimated separately for HBeAg positive and negative patients.

4.1.1 Manufacturer's review of published economic evaluations

A review of the use of nucleos(t)ides in the treatment of CHB is presented section 7.1 of the MS, with further details of the search strategy given in MS Appendix 2 . The search strategy aimed to identify all papers relating to the use of tenofovir, entecavir, telbivudine, lamivudine and/or adefovir dipivoxil in the treatment of chronic hepatitis B. All economic analyses identified by the search were flagged and examined to assess whether they met two additional inclusion criteria, which specified that studies were included if they:

- evaluated tenofovir monotherapy
- evaluated both costs and benefits.

A total of 1,272 publications were identified by the search, of which two met the inclusion criteria.[28,29] These studies, by the same lead author, described a cost-effectiveness simulation of tenofovir compared to other treatments in Spain, Italy and France. These analyses found that first-line use of tenofovir generated more quality-adjusted life years (QALYs) and reduced medical costs compared with first-line use of lamivudine, adefovir or entecavir in all three countries evaluated.

4.1.2 Cost-effectiveness analysis (CEA) Methods

The manufacturer's cost-effectiveness analysis uses a Markov state transition model that included 11 distinct disease states. The model has a lifetime horizon and a cycle length of one year, with a half-cycle correction applied. The model incorporates first-, second- and third-line treatments. Patients move on to the next treatment regime when they develop resistance to their current treatment.

The deterministic base case analysis compares 211 different treatment pathways covering all logically-plausible sequences of the eight antiviral treatments/treatment combinations (tenofovir, lamivudine, adefovir, entecavir, adefovir + lamivudine, tenofovir + lamivudine, entecavir + adefovir and best supportive care (BSC)). The results are presented for HBeAg positive and negative patients reporting total cost and QALYs for each strategy and incremental cost-effectiveness ratios (ICERs) between treatment strategies (MS Table 35-38).

4.1.2.1 Natural history

The natural history model allows patients to experience improvement in their condition (by HBeAg seroconversion, where relevant, or by HBsAg seroconversion) or to experience progression to advanced liver disease. Viral load is a key influence on disease progression in the model. Based on current clinical opinion and published evidence,[19,30,31] progression to compensated cirrhosis and to advanced liver disease is lower for chronic CHB patients with lower viral load. In the model, treatment with nucleos(t)ide analogues has the effect of increasing the probability of viral suppression and, where relevant, HBeAg seroconversion above the levels observed in untreated patients.

4.1.2.2 Treatment effectiveness

Estimates of treatment effect, in terms of viral suppression and HBeAg seroconversion, were derived from a Bayesian MTC, reported in section 6.6 and AIC Appendix 4 of the MS (and appraised by the ERG in section 3.1.6 of this report). The MS also reports a pooled analysis used to derive risk of resistance to treatment (MS section 6.10.1 and Appendix 5). These are discussed further in section 4.3.2.2 of this report.

The model does not include adverse effects, in terms of impact on quality of life, treatment compliance or cost. The MS states that tenofovir has been shown to be at least as well as tolerated as adefovir and placebo and that most side-effects have little impact on quality of life or cost. This assumption has been applied for all nucleos(t)ide analogues included in the model.

4.1.2.3 Health related quality-of-life

The model assumes that health states corresponding to the stages of natural disease progression determine patients' quality of life. This is consistent with previously published economic evaluations.[32] Utility values applied in the model were taken from a recent study by Ossa and colleagues[33] in which values were directly elicited from patients with CHB and from a group of uninfected participants, using the standard gamble technique.

4.1.2.4 Resources and costs

The healthcare resource use associated with CHB were calculated in two ways. For the least severe disease states, resource use estimates were based on those used in the independent Technology Assessment Report (TAR) used in the NICE appraisal of pegylated interferon alfa-2a and adefovir for CHB [32] supplemented by expert opinion. Unit costs were also taken from the TAR,[32] as well as from published tariffs and standard references.[34] For the more severe disease states, costs were taken from previous economic evaluations which have included detailed costing studies for patients in these states.[35,36]

4.1.2.5 Discounting

An annual discount rate of 3.5% was applied to both costs and outcomes.

4.1.2.6 Sensitivity analyses

The MS reports deterministic sensitivity analyses conducted by varying parameters between what were considered to be minimum and maximum plausible values (MS section 7.3.3.1.3 and MS section 7.3.3.1.4). The MS presents tornado diagrams that show those parameters with the most effect on the model results (MS Figures 16-18). The sensitivity analyses showed the model results were generally robust to changes in the parameter values.

The MS reports probabilistic sensitivity analyses (PSA) including 20 treatment strategies that were regarded as the most plausible options. The results for the PSA are shown in Table 42 and Table 43 of the MS, and in Figures 9 to 15. The MS concludes, based on these analyses, that there is a 60% and 58% probability that first-line tenofovir monotherapy is the most cost-effective antiviral strategy for HBeAg positive and negative patients respectively at a £20,000/QALY threshold. However, the ERG has discovered several presentation errors in the MS for the PSA and sensitivity analyses and these are discussed in more detail in section 4.3.4.

4.1.2.7 Model validation

The MS states that assumptions used in the model were validated by seeking the opinion of clinical specialists in this area. Ten clinicians and one specialist nurse were interviewed. Furthermore, the MS reports that the model and economic evaluation has been subjected to

internal validation and error checking. However, the ERG found several errors in the model and these are discussed in more detail in section 4.3.3.

4.1.2.8 Results

The MS presents base case results in MS section 7.3 as incremental cost per QALY gained (Tables 35 to 38 of the MS). The deterministic base case analysis compares 211 different treatment pathways. Table 17 and Table 18, below, summarise the results reported in the MS. These tables only show those strategies that would lie on the cost-effectiveness frontier.

Table 17 Base case results for HBeAg-positive patients

Treatment strategy	Total QALYs/ patient	Total cost/ patient	Cost/ QALY vs LAM then BSC	Cost / QALY vs next best on the cost-effectiveness frontier
BSC	16.81	£9,483	-	-
LAM then BSC	17.42	£12,899	-	£5,549
LAM then TDF	18.84	£21,463	£6,014	£6,014
TDF then LAM	19.57	£28,718	£7,344	£9,940
TDF then TDF+LAM	19.60	£29,040	£7,412	£10,055[†]
TDF then TDF+ LAM then ETV	19.60	£29,041	£7,413	£36,583

Notes:
the cost-effectiveness frontier indicates optimal treatment strategies – those which provide a given output at minimum cost. Points above the cost-effectiveness frontier are excluded, since the same output can theoretically be provided at lower cost by a combination of strategies that are found on the frontier.
[†] this value, which is reported in the MS, is the incremental cost-effectiveness of TDF then TDF+LAM compared with LAM then TDF, not TDF then LAM (which is the appropriate comparator on the cost-effectiveness frontier). ICER for TDF then TDF+LAM compared with TDF then LAM is £13,619

The key differences between the model results for the HBeAg positive and HBeAg negative cohorts, presented in the MS, is the total QALYs associated with each intervention are substantially lower for the HBeAg negative cohort compared with the HBeAg positive cohort (for example 11.75 compared with 16.81 for BSC, respectively). This reflects the poorer prognosis for patients with HBeAg negative CHB, given the higher probability of progressing to compensated cirrhosis (9% compared with 5% for the HBeAg positive cohort). Total costs associated with each intervention are substantially higher for the HBeAg negative cohort

compared with the HBeAg positive cohort (for example £60,079 compared with £28,718 for tenofovir followed by lamivudine). This reflects the fact that HBeAg negative patients cannot achieve HBeAg seroconversion, and there is therefore limited opportunity for ceasing anti-viral therapy. While treatment strategies including lamivudine are retained in the analysis for HBeAg positive patients, for HBeAg negative patients strategies including tenofovir dominate (by strict or extended dominance) strategies adopting other agents for first-line therapy.

Table 18 Base case results for HBeAg-negative patients

Treatment strategy	Total QALYs/ patient	Total cost/ patient	Cost/ QALY vs BSC	Cost/QALY vs next most effective strategy on frontier
BSC	11.75	£14,331	-	-
TDF then LAM	16.41	£60,079	£9,811	£9,811
TDF then TDF+LAM	16.51	£61,455	£9,895	£13,854
TDF then TDF+LAM then ETV	16.51	£61,460	£9,896	£20,781

The MS states that first line use of tenofovir monotherapy is the most cost-effective antiviral strategy for managing both HBeAg positive and negative CHB if the NHS is willing to pay between £20,000 and £30,000 per QALY gained. Furthermore first line use of tenofovir monotherapy is less costly and generates more QALYs than first line use of entecavir, adefovir or combination therapy.

The ERG has found several errors in the electronic model submitted as part of this assessment and in the presentation of results in the MS. These are detailed in section 4.3.3.1, which also contains an amended set of results calculated by the ERG.

4.2 Critical appraisal of the manufacturer's submitted economic evaluation

4.2.1 Critical appraisal of economic evaluation methods

The ERG has considered the methods applied in the economic evaluation in the context of the critical appraisal questions listed in Table 19 below, drawn from common checklists for economic evaluation methods (e.g. Drummond and colleagues[37]).

Table 19 Critical appraisal checklist of economic evaluation

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	Yes	
Is there a clear description of alternatives?	Yes	• The model considers possible treatment strategies including currently licensed nucleos(t)ide analogues (excluding telbivudine which is not recommended by NICE), including combination treatment and BSC. • Allowable treatment sequences were defined on the basis of a set of rules reported on page 97 of the MS. • Only three combinations were considered (adefovir+lamivudine, entecavir+adefovir and tenofovir+lamivudine) based on discussion with clinical experts and advisory board (see MS page 96).
Has the correct patient group / population of interest been clearly stated?	Yes	See section 7.2.2.1 of the MS – "HIV negative adults with CHB, who have compensated liver function, evidence of viral replication, persistently elevated serum alanine aminotransfereases or histologically active disease" - based on licensed indication. Baseline population (age and distribution across disease stages) based on a small scale audit of a UK liver clinic. Expert clinical opinion sought by the ERG suggests that these distributions seem generally reasonable However, natural history studies have suggested that patients with HBeAg negative CHB would be older (median age of 31 vs 40) and would have higher proportion with cirrhosis than patients HBeAg positive CHB. Some discussion of this in the MS, but needs testing in scenario analyses. Patient group is in agreement with the scope, by: • focussing on marketing authorisation; • excluding patients co-infected with hepatitis C, hepatitis D or HIV. Subgroups considered: • HBeAg positive and HBeAg negative cohorts (referred to as subgroups in MS) • Lamivudine-resistant (this analysis severely

		hampered by sparsity of data)
Is the correct comparator used?	Yes	MS has justified exclusion of interferons. MS has justified exclusion of telbivudine (see MS section 7.2.3): • Telbivudine is not recommended by NICE;
Is the study type reasonable?	Yes	Cost-utility model is appropriate for patients with CHB as quality of life differences are important as well as life expectancy differences. Previous evaluations have shown small differences in life expectancy for anti-viral treatment strategies.
Is the perspective of the analysis clearly stated?	Yes	Study perspective stated as that of NICE reference case (MS section 6.2.4, page 79)
Is the perspective employed appropriate?	Yes	• Costs from NHS and PSS perspective. • Outcomes from patient perspective –quality-adjusted life expectancy.
Is effectiveness of the intervention established?	Yes – for some comparisons	• For nucleos(t)ide naïve HBeAg positive and negative patients compared with adefovir - direct evidence from RCTs [4,5] • For comparison with other nucleos(t)ide analogues an MTC was conducted – providing reliable results for HBeAg positive nucleos(t)ide naïve patients only. Inconclusive results for HBeAg negative nucleos(t)ide naïve patients and lamivudine-refractory patients.
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	Yes	Lifetime horizon is appropriate given nature of disease and potential lifetime duration of treatment
Are the costs and consequences consistent with the perspective employed?	Yes	
Is differential timing considered?	Yes	Model has applied correct discount rates, following NICE methodological guidance. However ERG has identified a serious error in the formulae used in discounting QALYs in the electronic model. As discussed in section4.3.3.1. The ERG has calculated the corrected base case estimates.
Is incremental analysis performed?	Yes	• Appropriate framework for analysis adopted – total costs and QALYs derived for each strategy. • From 211 treatment strategies, alternatives were eliminated using cost-effectiveness frontier and dominance/ extended dominance. • ICERS were calculated relative to a fixed baseline (LAM then BSC for HBeAg positive cohort, and BSC for HBeAg negative cohort) and relative to next best option on the cost-effectiveness frontier.

Is sensitivity analysis undertaken and presented clearly?	Yes	• Univariate sensitivity analyses, scenario analyses and PSA were undertaken. Generally well presented. • Deterministic (univariate) sensitivity analyses presented in tornado plots (MS Figure 16 and 17 for selected strategies in HBeAg positive cohort; MS Figure 18 for TDF then LAM relative to BSC in HBeAg negative cohort). • Scenario analyses presented in tables (MS Table 44 and 45 for HBeAg positive cohort; MS Table 46 and 47 for HBeAg negative cohort). • PSA presented as scatterplots, tables and CEACs (MS Figures 9 to 11, MS Table 42 and MS Figure 12 for HBeAg positive cohort; MS Figures 13 to 14, MS Table 43 and MS Figure 15 for HBeAg negative cohort). • As discussed in sections 4.3.3.1 and 4.3.4.5 of this report, a number of errors were discovered in the presentation and analysis for the PSA. Requests for clarification were sent to the manufacturer for some of the errors (see Response Appendix F). Further analyses were undertaken by the ERG and are reported in section 4.3.4.6.

NICE reference case

Table 20 NICE reference case requirements

NICE reference case requirements (see detail in NICE report)**:**	Included in Submission
Decision problem: As per the scope developed by NICE	✓[$]
Comparator: Alternative therapies routinely used in the UK NHS	✓[&]
Perspective on costs: NHS and PSS	✓
Perspective on outcomes: All health effects on individuals	✓[#]
Type of economic evaluation: Cost-effectiveness analysis	✓
Synthesis of evidence on outcomes: Based on a systematic review	✓[†]
Measure of health benefits: QALYs	✓
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	×*
Method of preference elicitation for health state values: Choice based method (e.g. TTO, SG, not rating scale)	✓
Source of preference data: Representative sample of the public	?[+]
Discount rate: 3.5% pa for costs and health effects	✓[‡]

Notes:
✓=yes; × = no; ? = uncertain; N/A=not applicable
[$] scope includes interferon (conventional and pegylated). Interferon was not included in the MTC or in the economic model – reasons for excluding interferon are discussed in section 7.2.3 of the MS and also in section 3.1.2 of this report.

[&] very large number of potential comparator strategies (211) many of which would not be considered for use in routine UK practice.
[#] model does not include adverse events. Discussed in MS (section 7.2.74) - mostly mild and not requiring formal intervention. This assumption seems reasonable and has been adopted in previous economic evaluations of nucleos(t)ide therapies.
[†] MTC for HBeAg seroconversion and viral suppression – but only to 52 weeks. Adjustment for results after one year. MTC only for HBeAg positive patients. Other data impacting on effectiveness (such as resistance) is taken from analyses other than MTC. There is not always evidence of systematic search for parameter values or quality assessment of studies providing data for input parameters.
* The utility values are taken from a study which used health state descriptions that were specific to liver disease and which were based on dimensions from Liver Disease Quality of Life Instrument, version 1.0[38] – hence cannot be considered as generic.
[+] utilities in the model are based on responses from liver clinic patients with HBV infection and some form of chronic liver disease (but not necessarily the state they were valuing). Study also reported valuations for uninfected individuals – although the representativeness of that population is not clear.
[‡] see section 4.3.3.1 for discussion of error in discounting calculation for QALYs

4.3 Critical appraisal of modelling methods in the manufacturer's economic evaluation

An outline critical review of modelling methods has been undertaken. The review has used the framework for good practice in modelling presented by Philips and colleagues[39] as a guide, addressing issues of model structure, structural assumptions, data inputs, consistency, and assessment of uncertainty.

4.3.1 Modelling approach / Model Structure

The model adopted for this submission was a Markov state transition model, which was evaluated using cohort simulation. The model is structurally similar to models adopted for previous economic evaluations of anti-viral treatment for CHB.[32,40-42] The state transition diagram for the model is presented in Figure 5, section 7.2.6.1 of the MS, and in the electronic model on the worksheet named *"Introduction"*. There is a discrepancy between the two versions of the transition diagram on the possibility of transitions from compensated cirrhosis to the chronic hepatitis state. A clarification was requested from the manufacturer, see Appendix, and this is discussed further in section 4.3.1.1.

The model consists of 11 distinct health states:

- HBsAg seroconverted
- HBeAg seroconverted
- **Viral suppression CHB (VS)**
- **Active CHB**
- **Viral suppression compensated cirrhosis**

- **Active compensated cirrhosis (CC)**
- **Decompensated cirrhosis**
- **Liver transplant**
- **Post-liver transplant**
- Hepatocellular carcinoma (HCC)
- Death

States marked in bold were duplicated in order to distinguish patients with HBeAg positive and HBeAg negative CHB (although transition probabilities in the model for decompensated cirrhosis, liver transplant and post-liver transplant states were identical for HBeAg positive and HBeAg negative patients). In addition the entire structure was replicated in order to retain a history of patients' resistance to previous therapy. The MS reports, in sections 7.2.6.3 and 7.2.7.5, that the model structure was informed by reviewing previous economic evaluations of anti-viral treatment for CHB.[32,43] The model structure was reviewed with clinical specialists. Clinical experts consulted by the ERG agreed that the model structure seemed reasonable.

Viral suppression is indicated by viral load less than 300 copies per ml – the lower limit of detection for viral assays commonly used in clinical trials and in routine practice. By contrast, active CHB is indicated by viral load greater than 300 copies per ml. This is an appropriate characterisation, as it allows the model to reflect the lower risk of disease progression for patients with viral suppression demonstrated in studies referenced in the MS,[19,30,31] without over-complicating the model with multiple viral load strata.

The model is structured to reflect the natural history of CHB in patients who have progressed beyond the immunotolerant phase (characterised by high levels of viral replication, but low levels of activity in the liver) to the immunoactive phase (characterised by lower levels of viral replication, but increased levels of ALT, moderate or severe liver necroinflammation and more rapid progression of fibrosis). Patients with compensated CHB (CHB or CC, with or without detectable virus) may experience improvements in their condition by undergoing HBeAg seroconversion (which indicates temporary remission of disease, but is only possible for patients with HBeAg positive CHB) or HBsAg seroconversion (which indicates permanent remission of disease). Alternately patients may experience disease progression by:

- development of cirrhosis (for those in CHB (active or VS) states);
- development of decompensated disease (for those in CC (active or VS) states).

In common with models adopted for previous economic evaluations of treatments for chronic hepatitis,[32,40-42] the model assumes that CHB patients need to progress to cirrhosis before experiencing decompensation.

Viral load is a key influence on disease progression in the model, with progression to compensated cirrhosis, and to advanced liver disease, being lower for CHB patients with lower viral load. It is assumed, in the model, that patients may experience spontaneous improvements in their condition (through HBeAg seroconversion) or reductions in viral load in the absence of any active anti-viral treatment. The effect of treatment with nucleos(t)ide analogues in the model is to increase the probability of viral suppression and, where relevant, HBeAg seroconversion above the levels observed in untreated patients. The model also allows for anti-viral treatment to have an impact on prognosis for patients, in some states, irrespective of viral load. For example, the mortality risk for an untreated patient with decompensated cirrhosis is 30% whereas for a treated patient the risk is 2.48%.

All individuals in the model – including those in the HBsAg seroconverted state – have an elevated risk of developing liver cancer (compared with never-infected individuals) but the risk is greater with disease progression. In addition, all individuals in the model are exposed to a background risk from all-cause mortality, unrelated to disease progression. Where a mortality risk, associated with being in a particular state in the model, is greater than the all-cause risk it is either applied as a state-specific excess mortality (for CHB (active and VS) and for compensated cirrhosis (active and VS)) or a higher state-specific total mortality risk is used (decompensated cirrhosis, HCC and liver transplant states).

It is assumed, in the model, that patients are eligible for initiation of treatment in the active CHB and active compensated cirrhosis states. This accords with the licensed indication for tenofovir. However, the model also assumes that patients who progress to decompensation would remain on treatment, irrespective of whether the anti-viral drug is licensed for treatment of patients with decompensated CHB. Currently, only lamivudine and adefovir have marketing authorisation for treatment of patients with decompensated liver disease. However, expert clinical opinion sought by the ERG suggests that it would be inappropriate to switch or withhold treatment from patients in this situation. Stopping or switching treatment could result in viral rebound with consequent worsening of the clinical condition.

The main criteria for stopping treatment include HBsAg seroconversion, HBeAg seroconversion, or the development of resistance to current anti-viral treatment. Patients who undergo HBeAg seroconversion in a given model cycle are assumed to continue treatment for six to twelve months (assumed at a mean of 10.2 months in the model) while patients undergoing HBsAg seroconversion continue treatment for an average of six months. EASL clinical guidelines suggest that consolidation therapy should be given preferably for 12 months following HBeAg seroconversion[2].

With respect to treatment resistance, the model assumes that virologic resistance (raised levels of HBV DNA) develops 10.5 months (on average) into each model cycle and that resistance is detected at the start of the next cycle following the development of resistance. Once virologic resistance has developed the patient's current treatment is no longer assumed to be more effective (in terms of viral suppression or, if relevant, HBeAg seroconversion) than BSC. In the model, it is assumed that once resistance has been detected, the patient changes treatment. They may either stop all active anti-viral treatment (switching to BSC), switch to an alternative anti-viral agent or add another agent to their current treatment – and the effectiveness parameters appropriate to their new treatment will be applied. Expert clinical opinion sought by the ERG suggests that the addition of another agent would be the most likely management strategy, and that stopping or switching would be inappropriate.

The assumptions, in the model, regarding the occurrence of treatment resistance and the frequency of monitoring, mean that patients with virologic resistance will be detected before they develop biochemical resistance (raised ALT). The MS uses this justification for not modelling the occurrence of ALT flares. Expert clinical opinion sought by the ERG suggests this is a reasonable assumption and would be the preferred approach to managing the emergence of drug resistance.

The model has a cycle length of one year, with a half-cycle correction applied. The MS refers to the model, which in the base case is run for 40 annual cycles, as having a lifetime horizon. However, given the comparatively low death rates applied in the model (1.07% for males and 1.09 for females) which are unrelated to patients' age, a sizable proportion of the cohort remain alive at the end of the simulation (only 62% of HBeAg positive cohort are dead under the base case assumptions when BSC is the treatment strategy). A clarification on the all-cause mortality

rates adopted was requested from the manufacturer (see Appendix), and this is discussed further in section 4.3.1.1

Sources of data used to develop/populate the model structure are specified, briefly in section 7.2.6.1.3 of the MS, with more detail in AIC Appendix 4 (for MTC on treatment effectiveness), Appendix 5 (for resistance), Appendix 9 (for transition probabilities used in the model) and Appendix 10 (for costs applied in the model). Key inputs on clinical-effectiveness (viral suppression and, where relevant, HBeAg seroconversion) were derived in an MTC (discussed in section 3.1.6 of this report). Risks of developing resistance to each anti-viral agent, transitions to compensated cirrhosis and HCC are derived from a range of sources and are not critically appraised in the MS (see section 4.3.2.2 of this report for further discussion of this).

4.3.1.1 Structural Assumptions

In common with models adopted in previous economic evaluations, loss of the surface antigen (HBsAg) is assumed to be a permanent cure. Patients in this state are assumed to have no risk of spontaneous reactivation of disease – though this does not imply that they have immunity from re-infection with hepatitis B. In contrast, patients losing the e antigen (i.e. HBeAg seroconversion) are at risk of spontaneous reactivation of disease (sero-reversion).

Differences between the model adopted for this submission compared with those from previous economic evaluations[32] include:

- This model includes a transition from HBeAg positive to HBeAg negative CHB. To date models have generally treated these two cohorts of patients entirely separately. In this model a proportion of patients with HBeAg positive CHB, but who have moved to the HBeAg seroconverted state, will reactivate disease and undergo a transition to HBeAg negative CHB. This accords with the view that HBeAg negative CHB is, for some patients, a later phase of the natural history of CHB. Clinical advisors to the ERG regard this as an appropriate assumption (i.e. that some patients develop HBeAg negative CHB on reactivation of disease from the HBeAg seroconverted state).
- This model assumes that probability of sero-reversion, from the HBeAg seroconverted state, is unrelated to the time spent in that state or whether the transition to HBeAg seroconversion was induced by treatment. Previously published economic evaluations have assumed that reactivation of disease may be more likely in the year following a treatment-induced HBeAg seroconversion.

The model treats viral suppression as a goal of treatment, in itself. This is appropriate for HBeAg negative patients. However, the model applies the same logic for HBeAg positive patients, suggesting that viral suppression is a goal of treatment, even in absence of HBeAg seroconversion, since it reduces the probability of disease progression. However, the rationale or clinical evidence for this assumption is not reviewed in the MS, although it does cite a large population based cohort study in Taiwan (the REVEAL study)[44] which supports the association between baseline viral load and the development of cirrhosis, hepatocellular carcinoma (HCC) and mortality. Expert clinicians consulted by the ERG note that other studies agree with this study, although few studies have included non-Asian patients.

There is a discrepancy between the transition diagram presented in the MS and in the electronic model. The transition diagram in the MS shows transitions from compensated cirrhosis (active or viral suppression) to the CHB (active or viral suppression) state whereas the version in the electronic model does not. Clarification was requested from the manufacturer (see Appendix) which stated that Figure 5 in the MS is correct, in that it allows for the possibility that patients may move from compensated cirrhosis to active CHB or VS, However the probability for this transition was set to zero in the base case. The ERG raised an additional concern over an implicit assumption of regression of cirrhosis for patients who undergo HBeAg seroconversion in the compensated cirrhosis state. In the model it is assumed that patients in the CHB or compensated cirrhosis states can achieve HBeAg seroconversion. However, it is does not track whether patients have entered the HBeAg seroconverted state from a CHB or compensated cirrhosis state. This means that patients can potentially move from compensated cirrhosis to HBeAg seroconversion then back to active CHB, essentially reversing cirrhosis. Expert clinical opinion sought by the ERG suggests that, while feasible, reversal of cirrhosis is uncommon. However, since seroconversion rates do not differ significantly between agents this is unlikely to bias results.

Patients enter the model with a diagnosis of CHB and may have developed compensated cirrhosis. Active CHB and active compensated cirrhosis are states in which treatment can be initiated. However treatment is not withdrawn from patients who progress beyond these states. The model assumes there may be benefits of anti-viral treatment, in terms of reduced risk of mortality, for patients in advanced liver disease states (see section 4.3.2.2). Patients receive anti-viral treatment until they undergo HBsAg seroconversion, achieve HBeAg seroconversion,

develop treatment resistance or die. Once patients develop resistance to their current anti-viral agent they may add a new agent, switch agents or cease anti-viral treatment depending on the treatment sequence being evaluated. As mentioned in section 3.1, it is unlikely in practice that treatment would be switched or would cease.

4.3.2 Data Inputs

4.3.2.1 Patient Group

Section 7.2.2.1 of the MS reports the patient group being modelled as HIV negative adults with CHB, who have compensated liver function, evidence of viral replication, persistently elevated serum alanine aminotransfereases or histologically active disease. This reflects the marketing authorisation for tenofovir. Patients with hepatitis C, hepatitis D or HIV co-infection were excluded from the analysis, as specified by the scope. (although, as mentioned in section 3.1.2, the manufacturer's systematic review of clinical-effectiveness permitted inclusion of RCTs in which up to 50% of patients were co-infected with HIV).

Characteristics of the baseline population of CHB patients eligible for anti-viral treatment in the model (in terms of age and distribution across disease stages) were based on a small scale audit of a London liver clinic. Expert clinical opinion sought by the ERG suggests that these distributions seem generally reasonable, although given that it is based on a London clinic it may not be representative in terms of ethnicity. The average age of patients in the model was assumed to be 38 years irrespective of HBeAg status. Natural history studies have suggested that patients with HBeAg negative CHB would be older (median age of 31 vs 40) and would have higher proportion with cirrhosis than patients HBeAg positive CHB. Similarly, the mean age of patients in Study 0102 (HBeAg negative patients) was higher than Study 0103 (HBeAg positive patients) (44 vs 34 years, respectively). The ERG asked the manufacturer to justify using the same age for both groups of patients. The manufacturer responded that this was done for simplicity, and that sensitivity analysis assuming different starting ages had no effect on conclusions (See Appendix).

There is no discussion, in the model outline in the MS, of the relevance of patients recruited to the RCTs or cohort studies (included in the MTC or other pooled analyses used to derive parameter inputs to the model) to the patient group specified for this analysis. It is therefore not entirely clear how appropriate the model input data are to the specified patient group.

The MS describes the key subgroups considered as cohorts of patients with HBeAg positive and HBeAg negative CHB. In addition the MS presents analyses for lamivudine-resistant patients. However this analysis is severely hampered by sparsity of data.

4.3.2.2 Clinical-effectiveness

As discussed in section 4.3.1 of this report, the model adopted for the economic evaluation is based on the natural history of CHB. The key effectiveness parameters in the model that are influenced by anti-viral treatment, are:

- probability of viral suppression
- probability of HBeAg seroconversion (for HBeAg positive patients).

These probabilities were estimated using a MTC (discussed in section 3.1.6).

One concern is that the MTC estimated effectiveness for one year of treatment only. Treatment outcomes for subsequent years are estimated by applying ratios, derived in a sub-set of six trials which reported data on viral suppression and HBeAg seroconversion at one and two years. These six trials are not identified in the MS and the appropriateness of this approach is not discussed. It is not clear which anti-viral agents were studied in these trials or whether all six trials were conducted in patients with HBeAg positive CHB – this may be inferred from the fact the same number of trials were used to derive the ratio for HBeAg seroconversion as for viral suppression.

While the MTC for HBeAg positive patients produced usable results, the analysis for HBeAg negative patients did not. As a consequence the clinical-effectiveness inputs to the model, for HBeAg negative patients, are based on a combination of data on HBeAg positive and HBeAg negative patients. This is not clearly identified in the main body of the MS – for example this is not clearly identified in section 7.2.6.1.3 of the MS which reports a summary of data inputs to the model – nor is the degree of uncertainty in the model results for this patient population adequately addressed.

Overall there is very limited discussion, in the cost-effectiveness section of the MS, of the key effectiveness parameters included in the model. While the MTC is presented in some detail in AIC Appendix 4, the relevance to the economic model is not discussed. Key uncertainties in model inputs that are not discussed include:

- The MTC included data for the first year of treatment only and could only be conducted for nucleos(t)ide naïve patients. The MTC is subject to certain methodological limitations, as discussed in section 3.1.6;
- Data used to derive ratios for viral suppression and HBeAg seroconversion (year 1 vs year 2) are not clearly reported in the MS. The same ratios are applied for all anti-viral agents.
- Data for nucleos(t)ide naïve HBeAg negative cohort are not based only on trials of HBeAg negative patients.

MS Appendix 5 shows the pooled analysis to derive the resistance probabilities. There is very limited discussion of the analysis in the main body of the MS. It is limited to describing the method used to infer resistance to tenofovir and the method for estimating resistance to combination therapy. The pooled analysis on resistance for treatment naïve patients includes up to nine studies (combining RCT, retrospective and prospective cohort studies and a previous pooled analysis) for lamivudine, six studies for adefovir (all RCT), and two each for tenofovir and entecavir. The MS reports that studies were identified from those included in the systematic review (reported in section 6.1 of the MS, with more detailed report in Appendix 2 of the MS), with additional inclusion criteria that studies should have reported appropriate resistance data and either included more than 100 patients or were existing pooled analyses. The criterion regarding size of study was subsequently relaxed, given the sparsity of data for some strategies (particularly combination therapies). The MS does not report any quality assessment or risk of bias with respect to included studies nor is there any discussion of the appropriateness of pooling data from studies with a variety of designs. The pooled analysis does not distinguish between resistance in HBeAg positive and HBeAg negative patients. Expert clinicians consulted by the ERG did not consider this to be a problem.

The pooled analysis was conducted by summing the number of patients reported as developing resistance and the total number of patients in each year of each included study (numbers were inferred in cases where values were not reported for each year separately). For lamivudine the proportions calculated for each year appear to have been interpreted as cumulative proportions. The MS does not report the method used to derive annual proportions – it appears that the annual probabilities have been derived by solving. For example, Table 1 in Appendix 5 of the MS estimates cumulative resistance to lamivudine to be 19.2% at the end of Year 1 and 37.0% at the end of Year 2, with an inference that the proportion of patients not resistant to lamivudine

at the start of Year 2 being 80.8% (i.e. 100% - 19.2%). The resistance rate for Year 2 can be estimated by solving the following equation for $resist_{Yr2}$

$$80.8\% \times resist_{Yr2} + 19.2\% = 37.0\%$$

This gives a value of 22.0% for the resistance rate for Year 2 – which is the value used in the model. Applying this approach to the cumulative resistance rates for Year 3 through to Year 5 (from Table 1 in Appendix 5 of the MS) yields the remaining values for lamivudine resistance used in the model. An alternative approach would be to use the same formula, as presented in section 7.2.12.1 of the MS - Table 21 shows the effect of applying this alternative calculation. The main impact would be to reduce the estimated risk of resistance in year 3 and increase risk of resistance in year 4.

Table 21 Alternative calculation of lamivudine resistance

Year	Lamivudine resistance in model	Lamivudine resistance alternative
1	0.1921	0.1921
2	0.2200	0.2062
3	0.3476	0.2564
4	0.1201	0.2245

In addition, values used in the model do not always correspond to those listed in Appendix 5 of the MS. For example, Appendix 5 reports that data from two studies (study 0103 and study 0104) have been used to estimate resistance to tenofovir with proportions [redacted] that correspond to figures in Table 25 in the MS, while values in the model are based on three studies (0103, 0104 and 903) [redacted]. This difference is unlikely to have substantially changed the model results.

The MS reports using data from a conference abstract to derive the relative risk of resistance with the combination of lamivudine and adefovir in HBeAg positive, nucleos(t)ide naïve patients. As mentioned earlier in Section 3.1.6, this trial has now reported in full (with two years of data) giving a less favourable set of results for combination therapy.[13] The data included in the abstract, and used in the model, reported 20% (10/49) of patients on lamivudine alone, developing resistance, whereas the proportion on combination therapy was 2% (1/49). In the full trial report 20% (10/51) and 43% (15/35) of patients on lamivudine alone had developed

resistance in year 1 and year 2 respectively, whereas 9% (5/58) and 15% (6/41) patients on combination therapy had developed resistance at the same time points. In contrast to the relative risk of 0.10 used in the model, the data presented in the full trial report give a relative risk of resistance of 0.44 at year 1 and 0.34 at year 2.

There is an inconsistency in the assumptions applied to estimate the effectiveness of combination treatments in the model. The MS states that, where evidence is lacking, the effectiveness of the combination treatment is made equal to the effectiveness of the most potent agent in the combination. However, one of the combinations included in the MTC (adefovir + lamivudine) shows poorer outcomes for viral suppression than for either of the included agents alone in treatment naïve patients, see Table 22.

Table 22 Estimated proportion of patients achieving viral suppression with lamivudine or adefovir alone versus the combination of lamivudine + adefovir

	LAM	ADV	LAM+ADV
HBeAg positive	0.3840	0.4885	0.3749
HBeAg negative	0.4688	0.6217	0.4539

Relative risks of progression for patients with viral suppression were estimated using data from an RCT of lamivudine for patients with histologically confirmed cirrhosis or advanced fibrosis[31], and two cohort studies[19,30], and are reported in Table 3, Appendix 9 of the MS). The relative risk of decompensation for cirrhotic patients who achieve viral suppression is different for treated and untreated patients (0.5209 compared with 0.2469) and is derived from a single study in each case (Liaw and colleagues[31] for treated patients, Fattovich and colleagues[30] for untreated). The MS does not discuss why the effect of viral suppression on progression in cirrhotic patients should differ between treated and untreated patients. Moreover, this assumption – that risk reductions associated with viral suppression may differ between treated and untreated patients - is applied inconsistently within the model. For example, a relative risk reduction (0.1695) is applied to the excess mortality probability for cirrhotic patients who achieve viral suppression under active treatment, but not for those receiving best supportive care (excess mortality of 5.1% for cirrhotic patients is assumed to reduce to 0.86% for those with viral suppression), while a contradictory approach is taken when applying a relative risk to the probability of patients in

the CHB state developing compensated cirrhosis. In the latter case the same relative risk, derived from the REVEAL-HBV study,[19] was applied to treated and untreated patients.

4.3.2.3 Patient outcomes

Utility values applied to health states in the base case model have been derived from published sources. For CHB, compensated cirrhosis and advanced liver disease states the model uses utility values reported by Ossa and colleagues[33,45] for patients chronically infected with HBV in the UK. General population norms reported by Kind and colleagues[46] were used for health states in the model that were not included in the study by Ossa and colleagues.[33,45]

In the study by Ossa and colleagues[33,45] two groups of respondents (infected patients attending a liver clinic and a cohort of uninfected participants) were presented with health state descriptions, based on dimensions from the Liver Disease Quality of Life Instrument, version 1.0.[38] While the conference poster by Ossa and colleagues, [33] reporting only data from UK respondents, does not present the health state descriptions used in the valuation exercise, these are included in the subsequent full publication of the multinational study, by Levy and colleagues.[45] Comparing these descriptions against common generic questionnaires used to assess health-related quality of life (for example, EQ-5D, SF-36 or Health Utilities Index - HUI) they contain items relating to:

- ability to perform usual activities, including social functioning;
- anxiety/ depression/ emotion;
- pain/ discomfort;
- energy;
- cognitive function/ confusion/ memory.

The health state descriptions do not contain any items that correspond to two of the EQ-5D/ HUI dimensions – mobility and self-care. It may be that these dimensions are less relevant to patients with CHB. However, the MS does not discuss the adequacy or comprehensiveness of the health state descriptions nor the extent to which the items correspond to validated, generic instruments available for assessing health-related quality of life. Items included in the health state descriptions, that are less commonly found in generic measures, relate to diet restrictions (due to advanced liver disease) and appetite. Items that may be regarded as entirely condition-specific are those related to requirements to attend primary or secondary care for tests, specific treatments or medication.

The health state descriptions were used in face-to-face interviews to elicit preferences using both visual analogue scales and standard gamble. Mean utilities, derived using each elicitation method, were calculated separately for each group of respondents (infected and uninfected). The standard gamble utilities, using responses from infected patients were used in the base case in the MS, while other valuations were included in scenarios analyses reported in Table 45 and Table 47 of the MS, for HBeAg positive and HBeAg negative patients respectively. Table 23 shows the mean standard gamble valuations and 95% confidence intervals for both the infected and uninfected groups.

Table 23 Health state utility values reported by Ossa and colleagues,[33] for patients chronically infected with HBV in the UK and uninfected respondents

	Infected mean (95% CI) n=93	**Uninfected mean (95% CI) n=100**
Chronic hepatitis B	0.77 (0.71 - 0.81)	0.82 (0.78 - 0.85)
Compensated cirrhosis	0.73 (0.65 - 0.77)	0.83 (0.80 - 0.87)
Decompensated cirrhosis	0.34 (0.25 - 0.39)	0.36 (0.30 - 0.42)
Liver transplant (1st Year)	0.56 (0.49 - 0.62)	0.71 (0.65 - 0.76)
Liver transplant (> 1st Year)	0.67 (0.59 - 0.73)	0.82 (0.78 - 0.86)
Hepatocellular carcinoma	0.36 (0.28 - 0.41)	0.46 (0.39 - 0.52)

In the model it was assumed that the presence of detectable virus had no effect on health state utility for the CHB and compensated cirrhosis health states. Hence the utility weights for "Active CHB" and "Viral suppression CHB (VS)" and for **"**Active compensated cirrhosis (CC)" and "Viral suppression compensated cirrhosis" were the same (0.77 for Active CHB and VS, 0.73 for CC and Viral suppression compensated cirrhosis).

Since the HBeAg seroconverted and HBsAg seroconverted states were not included in the study reported by Ossa and colleagues[33,45] the MS adopted a population norm estimated in a large population sample, reported by Kind and colleagues,[46] derived using the EQ-5D and valued using the UK Time Trade Off (TTO) tariff.[47] The MS used the mean value weighted across all age groups of 0.86 – this compares with an age-group specific mean of 0.91 for the 35-44 age group (relevant to the starting age of 38 for the modelled cohort), declining to 0.73 for the 75+ age group. Adopting the mean value across all ages (0.86) suggests a health state

utility gain of 0.09 for achieving HBsAg seroconversion from the Active CHB or VS states, if using the valuations from infected patients, and a health state utility gain of 0.06 if using the valuations from uninfected respondents. Adopting an assumption from Wong and colleagues[42] a weighting of 0.99 was applied to the population norm value to estimate the health state utility for the HBeAg seroconverted health state. This corresponds to a utility weight of 0.85 for the HBeAg seroconverted health state. The full set of health state utilities adopted in the base case of the model are shown in column 4 (headed "Infected respondents") of Table 24.

The health state utilities adopted for the base case in the MS are broadly comparable to those used in the previous independent Technology Assessment Report (TAR) used in the NICE appraisal of pegylated interferon alfa-2a and adefovir for CHB, [32] though the approach to applying health state utilities differed. The model developed for the TAR used age-specific population norms, reported by Kind and colleagues,[46] for both the HBsAg and HBeAg seroconverted health states and applied state-specific utility decrements for the CHB, compensated cirrhosis and advanced liver disease states. The main difference between the two sets of utility values, that would be likely to have an impact when evaluating treatments in a cohort of patients with CHB and compensated liver function, concerns the health state utility value for compensated cirrhosis. The utility values for compensated cirrhosis and advanced liver disease states, adopted in the assessment of pegylated interferon alfa-2a and adefovir, were based on published EQ-5D valuations for patients with chronic hepatitis C, and assume a large utility loss associated with progressing from CHB to compensated cirrhosis and a smaller reduction when progressing to decompensated liver disease, see Table 24. The reverse is the case in the valuations reported by Ossa and colleagues.[33,45]

The health state utilities reported Ossa and colleagues[33,45] appear to be appropriate for modelling the effect of anti-viral treatment of CHB, although they do not strictly meet the NICE reference case (see Table 20 of this report) which stipulates that public, rather than patient, preferences should be used in health state valuation.

Table 24 Health state utilities used in economic evaluations

	adefovir NICE TAR[32]		Ossa and colleagues[33,45]	
Health state	**State-specific utility**	**Health state utilities**	**Infected respondents[33,4]**	**Uninfected respondents[33,4]**

	decrements		5	5
HBsAg seroconverted	0.00	0.86	0.86	0.86
HBeAg seroconverted	0.00	0.86	0.85	0.85
Chronic hepatitis B	0.04	0.82	0.77	0.82
Compensated cirrhosis	0.44	0.42	0.73	0.83
Decompensated cirrhosis	0.54	0.32	0.34	0.36
Hepatocellular carcinoma	0.54	0.32	0.36	0.46
Liver transplant	0.55	0.31	0.56	0.71
Post-liver transplant	0.32	0.54	0.67	0.82

The MS presents an analysis using the health state valuations from the uninfected respondents, in Table 45 of the MS for HBeAg positive patients and in Table 47 of the MS for HBeAg negative patients. These generally show marginal lower ICERs when applying the health state valuations from uninfected respondents. It is not entirely clear how representative the sample of uninfected individuals included in the study by Ossa and colleagues[33,45] are (see Table 25 below). However, this is the only known published study to directly estimate utilities for health states relevant to CHB using a preference-based method. Use of valuations from the conference poster (Ossa and colleagues[33]) rather than the full publication (Levy and colleagues[45]) is appropriate since the former reports only UK data, which includes 95% confidence intervals. In contrast, while the full publication reports point estimates for UK respondents it does not report standard errors or 95% confidence intervals.

Table 25 Socio-demographic characteristics of infected and uninfected respondents in study reported by Ossa and colleagues[33]

Characteristic	Infected subjects (n=93) Percentage	Uninfected subjects (n=93) Percentage

Male	58.9	47
Race		
White	33.7	94
Black	29.0	1
Asian	22.8	5
Other	15.1	0
Marital status – married/common-law	85.2	76.7
Employment – full time	62.4	46.5
Education – continued after 16	76.4	76

4.3.2.4 Resource use

Three types of resource were identified and costed in the MS (see section 7.2.9 of the MS for details):

1) Drug acquisition
2) On-treatment monitoring and management
3) Health state costs – associated with post-treatment surveillance of patients with chronic disease as well as symptomatic management of advanced liver disease states

Treatment costs have been calculated using the licensed dosage for each anti-viral agent (see Table 26). Drug costs per year of treatment were calculated, in line with the annual cycle adopted for the Markov model. Costs of consolidation treatment for patients undergoing HBeAg or HBsAg seroconversion were adjusted pro rata to the assumed duration of consolidation treatment (10.2 months for HBeAg seroconversion and 6 months for HBsAg seroconversion).

Resource estimates used for mild CHB states were based on treatment protocols developed for the TAR used in the NICE appraisal of pegylated interferon alfa-2a and adefovir for CHB. [32] The protocols were reviewed by clinical specialists and updated where relevant.

Table 26 Resource use assumptions for anti-viral drugs in MS

Cost per year of treatment[†]	Price per pack (£)	Packaging	Licensed dosage	Anti-viral drug
1,018.35	78.09	28 x 100mg tablets	100 mg/ day	Lamivudine

3,835.13	315.00	30 x 10mg tablets	10 mg/ day	Adefovir
4,599.00 4,599.00	378.00 378.00	30 x 0.5mg tablets 30 x 1.0mg tablets	0.5 mg/ day‡ 1.0 mg/ day	Entecavir
3,787.25	290.33	28 x 600mg tablets	600 mg/ day	Tenofovir
Notes † assumes average year of 365 days ‡ the recommended daily dosage of entecavir is 0.5 mg for nucleoside naïve patients and 1.0 mg for lamivudine-resistant patients				

It appears from the MS that the resource use protocols were originally developed in collaboration with two Scottish hepatologists, which were supplemented by discussion with three specialists practicing in England [redacted]. These concluded that treated patients would typically be seen in clinic every 3-6 months, which is less frequently than was assumed in the TAR.[32] As a result health state costs for the mild states are lower than were estimated in the previous assessment report, see Table 27.

Table 27 Health state costs used in economic evaluations

Health state	Health state costs from adefovir NICE TAR[32] (£)	Health state costs in MS
HBsAg Seroconversion	0	99.39
HBsAg Seroconversion	267	191.51
CHB - untreated	537	303.03
CHB / VS - treated	537	422.01

Health state costs for severe disease states (cirrhosis (compensated and decompensated), hepatocellular carcinoma and liver transplantation) adopted in the model are taken from an HTA monograph reporting an economic analysis conducted for the UK Mild Hepatitis C RCT.[35] Health state costs for compensated cirrhosis, decompensated cirrhosis and HCC were based on an observational study (conducted alongside the UK Mild Hepatitis C RCT) which recruited patients who attended any of three study hospitals for an inpatient admission related to hepatitis C, or for an outpatient appointment at the liver clinic, between 30 March 1998 and 1 April 2000. Costings were based on data in patients' case notes, and from hospital histopathology, virology and pathology databases. Health state costs for the liver transplant and post-liver transplant states were taken from an unpublished study conducted for the Department of Health,[36] which

was also used to cost these states in the UK Mild Hepatitis C RCT. Costs for hepatitis B immune globulin (HBIG) provided to liver transplant patients were added to the health state costs for both the liver transplant and post-liver transplant states, based on expert opinion. The MS discusses the appropriateness of applying costs of advanced liver disease estimated for patients with chronic hepatitis C to CHB. This seems a reasonable approach and retains compatibility with assumptions adopted for TAR used in the NICE appraisal of pegylated interferon alfa-2a and adefovir for CHB. [32]

4.3.2.5 Costs

Unit costs for all anti-viral drugs are taken from the British National Formulary (BNF 54, published September 2007).[48] These unit costs are unchanged in the current BNF (No 56 published September 2008).[49] Other unit cost data (cost of patient assessments while on-treatment and mild disease state costs) were taken from a previous economic evaluation,[32] published tariffs and standard references[34] and, where appropriate, have been uprated to 2006/07 prices, using the Hospital and Community Health Services (HCHS) Pay and Prices Index.[34] Unit costs for severe disease states were taken from an HTA monograph reporting an economic analysis conducted for the UK Mild Hepatitis C RCT[35] and have been uprated from 2002/03 to 2006/07 prices, using the HCHS Pay and Prices Index.[34]

4.3.3 Consistency

4.3.3.1 Internal consistency

The electronic model is coded in MS Excel and is fully executable. It contains several worksheets, including a deterministic analysis, sensitivity analysis and PSA. The deterministic analyses are run from the 'Results' worksheet. A treatment strategy can be defined in terms of first, second and third line treatment and the results are generated on this sheet. Random checking of the model has been done for some of the key equations in the model. However, the ERG has not undertaken a comprehensive check of all cells in each model. The ERG has checked samples of the input data and these correspond with data inputs specified in the main submission and appendices.

The model is generally poorly presented, with little or no documentation of its design or how to use it. For example, there are several sheets where it is possible to run results from and duplicate sheets of the Markov engine, transition probabilities and other sheets. Upon request,

the manufacturer provided descriptions of the model and instructions on how to run it and these are shown in the Appendix. The model contains over 200 scenarios and parameter values for the sensitivity analysis. Whilst comprehensive, running the model with all these scenarios is very time consuming. For example, running the model for the deterministic scenarios takes over fifteen minutes on a computer with processing speed of 2.8 MHz. As shown in the MS, most of these scenarios are unlikely to be relevant and the ERG suggests running the model with only most relevant scenarios.

There is no report in the MS, nor any evidence in the submitted models, of any checks conducted by the manufacturer of the accuracy of input data in the models.

Errors identified by the ERG in the model

i) QALYs were incorrectly discounted in the MS model, so that discount factors are only applied in half of the model cycles (only for odd-numbered cycles, with undiscounted values for even-numbered cycles). The corrected values for HBeAg positive patients, calculated by the ERG, are shown in the final column of Table 28. A similar error exists in the presentation of the base case results for HBeAg negative patients – these have been omitted from this report for brevity. However, a full set of corrected base results for HBeAg positive and HBeAg negative patients (replicating Tables 36 and 38 in the MS, but taking into account all errors detected by the ERG in the submission) are presented at the end of this section (see Table 31 and Table 32 in this section) and discussed in section 4.3.5.

Table 28 Inconsistent base case results from MS (HBeAg positive patients) and ERG correction

Strategies	Undiscounted (MS)		Discounted (MS)		Discounted (ERG)	
	Life Years	QALY	Life Years	QALY	Life Years	QALY
BSC then BSC	25.45	20.68	15.75	16.81	15.75	12.69

LAM then BSC	26.28	21.46	16.18	17.42	16.18	13.13
LAM then TDF	28.53	23.37	17.18	18.84	17.18	14.02
TDF then LAM	29.62	24.33	17.69	19.57	17.69	14.50
TDF then TDF+LAM	29.66	24.36	17.71	19.60	17.71	14.51
TDF then TDF+LAM then ETV	29.66	24.36	17.71	19.60	17.71	14.51

ii) As discussed in section 4.3.2.2, a lower excess mortality risk is applied to patients with compensated cirrhosis who have undetectable HBV DNA compared with those with detectable HBV DNA. It appears that the estimated risk reduction of 0.17 has been applied twice in the electronic model – once in cell E19 on the worksheet named *"Efficacy (2)"* and again in the transition matrices on the worksheet named *"TP Tables (2)"*. Removing this double-counting has a marginal effect on the cost-effectiveness results (see Table 29).

Table 29 ERG correction of base case results, removing double application of reduction of excess mortality for patients with compensated cirrhosis achieving viral suppression (HBeAg positive patients)

	Life Years	QALYs	Costs	ICER
BSC then BSC	15.75	16.81	£ 9,483	
LAM then BSC	16.18	17.42	£ 12,891	£ 5,575
LAM then TDF	17.15	18.80	£ 21,312	£ 6,093
TDF then LAM	17.63	19.50	£ 28,467	£ 10,269
TDF then TDF+LAM	17.64	19.52	£ 28,779	£ 14,182
TDF then TDF+LAM then ETV	17.64	19.52	£ 28,781	£ 40,516
Note that the ICER for TDF then TDF+LAM reported here should be compared with the corrected value of £13,619 reported at the bottom of Table 17, for consistency.				

iii) There is an inconsistency between MS Table 37 and MS Table 38 in the submission (and between MS Table 37 and the submitted electronic model). The inconsistencies are as follows:

- The row labels in MS Table 37 are consistent with MS 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 MS Table 38 are consistent with the submitted electronic model.

The manufacturer provided an amended table in their response to ERG questions (see Appendix).

iii) The cost-effectiveness acceptability curves presented in Figure 15 of the MS, for the HBeAg negative population, were not correct (or consistent with data for the deterministic base case presented in MS Table 38). The manufacturer provided an amended PSA in their response to ERG questions (see Appendix).

iv) There were 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 showed that calculations to derive mean ICERs (in cells DY4 to ER4 on the "Simulations" sheet) were based on maximum values (derived in cells H4 to DW4 the "Simulations" sheet) rather than averages. The manufacturer provided an amended analysis in their response to ERG questions.

v) When running the PSA for the submitted electronic model there were errors in approximately 4% of simulations for some of the included treatment strategies. The manufacturer confirmed these errors in their reply to the ERG request for clarification (see Appendix). Due to these errors, it was not possible to construct Cost-effectiveness acceptability curves (CEACs) without excluding those simulations which generated errors.

vi) A series of deterministic sensitivity analyses can be run by clicking on the 'Tornado diagram' on the 'Data and references' worksheet. This calculates the results for all parameters and orders the impact of these parameters. However there is an error in the model which causes this analysis to fail. One of the parameters (Std consult (on Tx): U & E) causes the error.

vii) The tenofovir resistance rates used in the model differ from those reported in Table 2 in Appendix 5 of the MS, as discussed in section 4.3.2.2.

viii) It was not possible to run the PSA for HBeAg positive patients without modifying the electronic model. This required the ERG to:

i) clear all default values for the proportion of patients starting in any of the health states (on the *"Data & References"* sheet in cells E222 to E237);

ii) enter a default value for the proportion of patients with active CHB (94.04%, see Table 30 in the MS) in cell E223 on the *"Data & References"* sheet;

iii) enter a formula (=1-U223) in cell U225 on the *"Data & References"* sheet (which contains the proportion of patients HBeAg positive patients entering the model with CC and detectable HBV DNA) to ensure that the proportion of patients entering the model correctly summed to unity.

ix) The transition matrices in the electronic model appear to have been constructed incorrectly for the CHB (active and viral suppression) and compensated cirrhosis (active and viral suppression) states. The effect of this error is to underestimate the probability of remaining in the current health state.

Table 30 below shows the impact of these errors on the probability of transitioning from the CHB Active to the CHB Active or to the CHB VS for the treatment strategies BSC, lamivudine and tenofovir.

These errors do not appear to bias the results, primarily because an ad hoc adjustment has been made to the transition matrix for tenofovir, in the model. However this is not an appropriate strategy to deal with an error in constructing the transition matrices and means that the matrices are inconsistent between strategies in the model.

Table 30 Correcting transition matrices in electronic model

Transition	BSC		Lamivudine		Tenofovir	
	MS	ERG	MS	ERG	MS	ERG
CHB Active=>HBsAg seroconversion	0.017500	0.017500	0.017500	0.017500	0.017500	0.017500
CHB Active=>HBeAg seroconversion	0.106900	0.106900	0.235400	0.235400	0.267400	0.267400
CHB Active=>CHB Viral suppression	0.000000	0.000000	0.141170	0.100750	0.636500	0.432817
CHB Active=>CHB Active	0.806495	0.806495	0.536825	0.577245	0.009495	0.213178
CHB Active=>CC Viral suppression	0.000000	0.000000	0.007430	0.007430	0.033500	0.033500
CHB Active=>CC Active	0.050000	0.050000	0.042570	0.042570	0.016500	0.016500
CHB Active=>Hepatocellular carcinoma	0.004826	0.004826	0.004826	0.004826	0.004826	0.004826
CHB Active=>Death	0.014279	0.014279	0.014279	0.014279	0.014279	0.014279

The ERG corrected these errors in the transition matrices on the worksheet named *'TP Tables (2)'*. However, given the number of tables and the complexity of the model calculations the ERG cannot be certain that all such errors were corrected.

The ERG amended the model in respect of the errors discovered and the results using the amended model are shown in Table 31 and Table 32. These analyses specifically correct for the errors in:

- discounting QALYs;
- double application of reduction of excess mortality for patients with compensated cirrhosis achieving viral suppression;
- construction of transition matrices.

The ERG analyses generally show treatment strategies to have less favourable ICERs than for the base case analyses reported in the MS. For HBeAg positive patients, total QALYs have reduced by 37%-39% while total costs have reduced by 12%-15%. The result of these changes is that the ICER for first-line tenofovir (followed by lamivudine if patients develop resistance to tenofovir) has approximately doubled – from £9,940 as reported in the MS to £17,590 in the ERG amended analysis. The ICER for tenofovir followed by lamivudine + tenofovir also approximately doubled – from £13,619 as reported in the MS to £27,479 in the ERG amended analysis.

Table 31 Amended base case results for the most cost-effective strategies in HBeAg-positive patients (replication of MS Table 25 with ERG corrections to the model).

Treatment strategy	Total QALYs/ patient	Total cost/ patient	Cost/ QALY vs LAM then BSC	Cost / QALY vs next most Effective strategy on frontier
BSC	10.59	£8,220	-	-
LAM then BSC	10.93	£11,411	-	£9,198
LAM then TDF	11.59	£18,194	£10,389	£10,389
TDF then LAM	11.95	£24,646	£12,979	£17,590
TDF then TDF+LAM	11.96	£24,877	£13,098	£27,479
TDF then TDF+	11.96	£24,878	£13,098	£92,354

Treatment strategy	Total QALYs/ patient	Total cost/ patient	Cost/ QALY vs LAM then BSC	Cost / QALY vs next most Effective strategy on frontier
LAM then ETV				

Table 32 Amended base case results for the most cost-effective strategies in HBeAg-negative patients (replication of MS Table 26 with ERG corrections model).

Treatment strategy	Total QALYs/ patient	Total cost/ patient	Cost/ QALY vs LAM then BSC	Cost / QALY vs next most Effective strategy on frontier
BSC	8.18	£12,439	-	-
TDF then LAM	10.30	£49,807	£19,791	£17,640
TDF then TDF+LAM	10.33	£50,794	£19,942	£28,324
TDF then TDF+ LAM then ETV	10.33	50,798	£19,943	£44,792

For HBeAg negative patients, total QALYs have reduced by 30% for BSC and 37% for strategies including active anti-viral treatment, while total costs have reduced by 13% and 17% for BSC and active treatment strategies, respectively. The result of these changes is that the ICER for first-line tenofovir (followed by lamivudine if patients develop resistance to tenofovir) compared with BSC has increased by approximately doubled – from £9,811 as reported in the MS to £17,640 in the ERG amended analysis. The ICER for tenofovir followed by lamivudine + tenofovir has approximately doubled – from £13,854 as reported in the MS to £28,324 in the ERG amended analysis.

All analyses undertaken by the ERG (reported in section 4.3.4.2, section 4.3.4.4 and section 4.3.4.6) included correction for the manufacturer's errors in discounting QALYs, in estimating the reduction of excess mortality for patients with compensated cirrhosis achieving viral suppression, and in the construction of transition matrices.

4.3.3.2 External consistency

The MS states that the model "has been subjected to internal validation and bug checking" but does not report any detail of the processes undertaken. Given this statement the ERG was surprised at the number of errors identified in the electronic model (see section above). The MS states that the key assumptions of the clinical pathways and resource use have been validated by clinicians. Furthermore, the MS states that the model has been adapted from previous submission to SMC and the All Wales Medicines Strategy Group and that both of these bodies had reviewed their methods, assumptions and the model produced.

The ERG notes that the MS does not compare its results with the previous NICE assessment of pegylated interferon alfa-2a and adefovir,[32] other submissions to NICE for antiviral treatment for CHB (e.g. entecavir), or previously published economic models, which would have provided external validation for their analyses.

4.3.4 Assessment of Uncertainty

4.3.4.1 One-way sensitivity analyses

A series of one way sensitivity analyses were carried out on the base case model by varying all parameters 'not known with certainty'. The MS conducted sensitivity analyses for tenofovir then lamivudine versus lamivudine then tenofovir; and lamivudine then tenofovir versus lamivudine then BSC for HBeAg positive patients. For HBeAg negative patients they compared tenofovir then lamivudine versus BSC. The ERG found the description of the comparators confusing as the comparators listed in the text differs from the comparison shown. For example, for HBeAg positive patients, the MS states that a first line tenofovir strategy is used against lamivudine but results for a second line tenofovir strategy are shown. Likewise, for HBeAg negative patients, the MS states that tenofovir is compared with BSC but the results for tenofovir then lamivudine versus BSC are shown.

For HBeAg positive patients, model results were most sensitive to: the probability of HBeAg seroconversion for anti-viral naïve patients receiving tenofovir, the probability of HBeAg seroconversion for lamivudine-resistant patients receiving tenofovir and the excess mortality associated with the viral suppression state. For HBeAg negative patients, model results were most sensitive to: the probability of developing compensated cirrhosis from the active CHB state, the discount rate for costs and the excess mortality associated with the viral suppression state. All other parameters had only minor effect on the model results with range between high and low parameter values of less than £5,000 per QALY gained.

The MS has justified the ranges used for all the parameters in the sensitivity analyses and these appear appropriate to the ERG. They state that parameters were varied over their 95% CI or the range of values that they could plausibly take. As mentioned above, there are some errors in the sensitivity analyses which meant the ERG was unable to run the sensitivity analyses with all parameters. However, the ERG was able to replicate the MS results with a smaller subset of parameters. The ERG suggests aggregating some of the parameters in the sensitivity analysis.

4.3.4.2 ERG sensitivity analysis

The ERG conducted one-way sensitivity analyses by varying all parameters between minimum and maximum plausible values, as specified in the MS, to produce tornado diagrams using the manufacturer's model with the corrections described above. Two sets of sensitivity analyses were run:

- First, the ERG replicated the sensitivity analyses reported in the MS (presented as tornado plots in Figures 16, 17 and 18 of the MS) with the corrections described in section 4.3.3.1 above. These are reported below in
- Figure 1, Figure 2 and Figure 3;
- Second, the ERG ran an additional sensitivity analysis – identifying which input parameters have the greatest impact on the cost-effectiveness results for the tenofovir then BSC strategy, relative to the lamivudine then BSC strategy, in HBeAg positive and HBeAg negative patients separately.

Replicating sensitivity analyses reported in the MS

When comparing the tornado diagrams produced by the sensitivity analysis, for HBeAg positive patients, using the corrected model (

Figure 1 and Figure 2) with those presented in the MS (Figures 16 and 17 in the MS) there are some striking differences. The degree of variability for the most influential variables (probability of HBeAg seroconversion with tenofovir) is substantially greater, as indicated by the change in scale of the X axis (from -£10,000 through £70,000 to -£50,000 through £350,000). It is also noticeable, in both figures, that the discount rate for outcomes has become more influential – moving up the ranking of parameters (in terms of sensitivity) from 10th in Figure 16 of the MS to 5th in

Figure 1, below, and from 7th in Figure 17 of the MS to 3rd in Figure 2, below. The range of values associated with changes in the discount rate applied to outcomes increases in absolute terms from £3,544 in Figure 16 of the MS to £15,673 in

Figure 1, below, and from £2,288 in Figure 17 of the MS to £10,731 in Figure 2, below. At the same time that the position of discounting of outcomes has increased, in terms of ranking of sensitivity, the ranking of model time horizon has reduced – from 5th in Figure 16 of the MS to 15th in

Figure 1, below, and from 6th in Figure 17 of the MS to 18th in Figure 2, below. The probability of viral suppression with tenofovir and the probability of progressing to cirrhosis from active CHB have also reduced their rankings in

Figure 1, compared with Figure 16 in the MS.

Figure 1 Corrected tornado diagram for impact of different variables on the cost effectiveness results for the tenofovir then lamivudine, relative to lamivudine then tenofovir in HBeAg positive patients (replicates Figure 16 of MS)

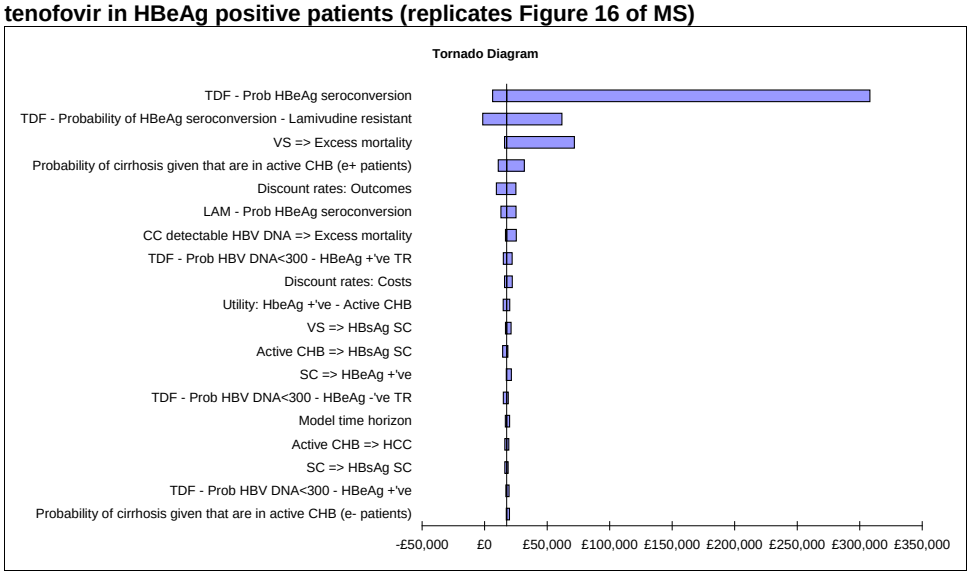


Figure 2 Corrected tornado diagram for impact of different variables on the cost effectiveness results for the lamivudine then tenofovir, relative to lamivudine then BSC in HBeAg positive patients (replicates Figure 17 of MS)

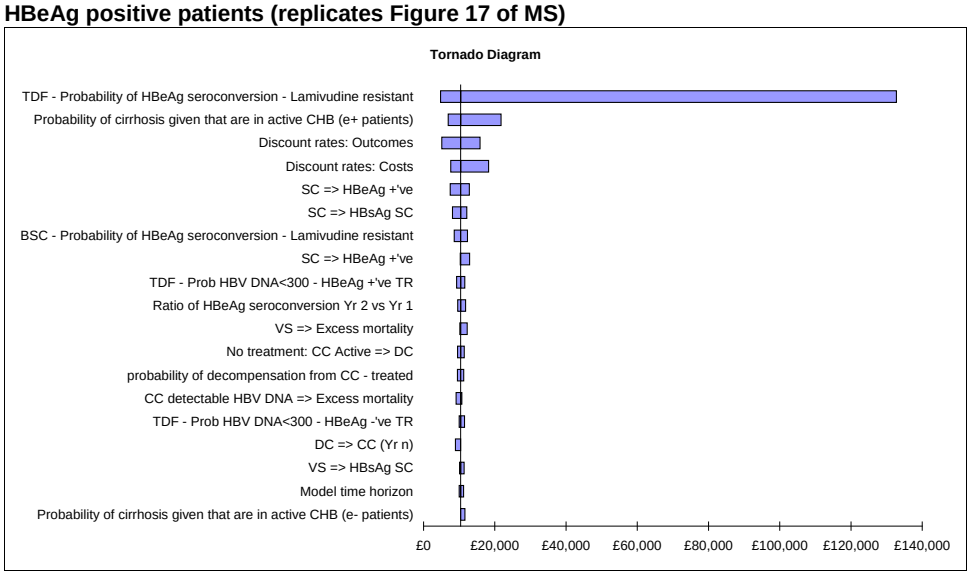
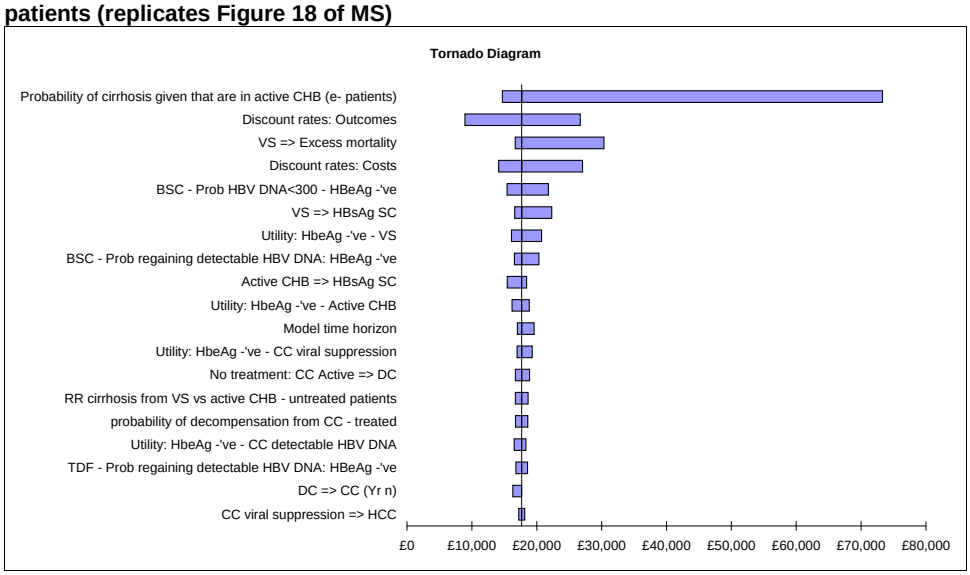


Figure 3, below, also shows greater variability, when compared with Figure 18 in the MS. However, the scale of difference is not as great as for the comparison of Figure 1 and Figure 2 with Figures 16 and 17, respectively, in the MS. Once again the ranking (5^{th} to 2^{nd}) and absolute range (from £3,711 up to £17,790) have increased in relation to changes in the discount rate for outcomes, while the ranking (4^{th} to 11^{th}) and absolute range (from £4,000 to £2,585) for variation in the time horizon have reduced. The probability of progressing to decompensation and the probability of regaining detectable virus when being treated with tenofovir have also reduced in the ranking of influential input parameters.

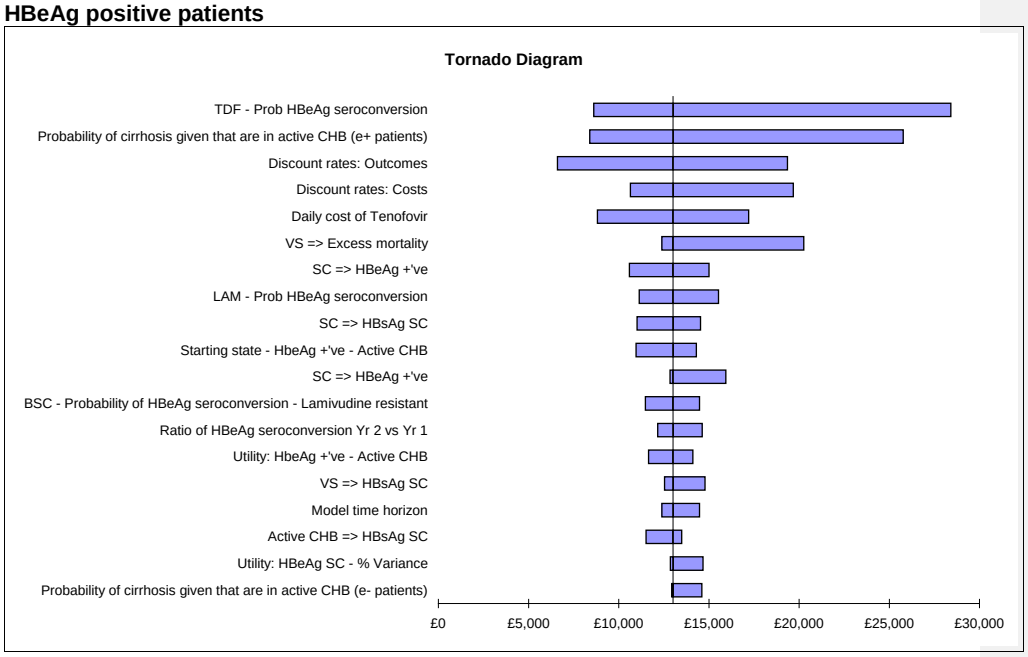
Figure 3 Corrected tornado diagram for impact of different variables on the cost effectiveness results for the tenofovir then lamivudine, relative to BSC in HBeAg negative patients (replicates Figure 18 of MS)



Additional ERG sensitivity analysis for the tenofovir then BSC strategy, relative to lamivudine then BSC

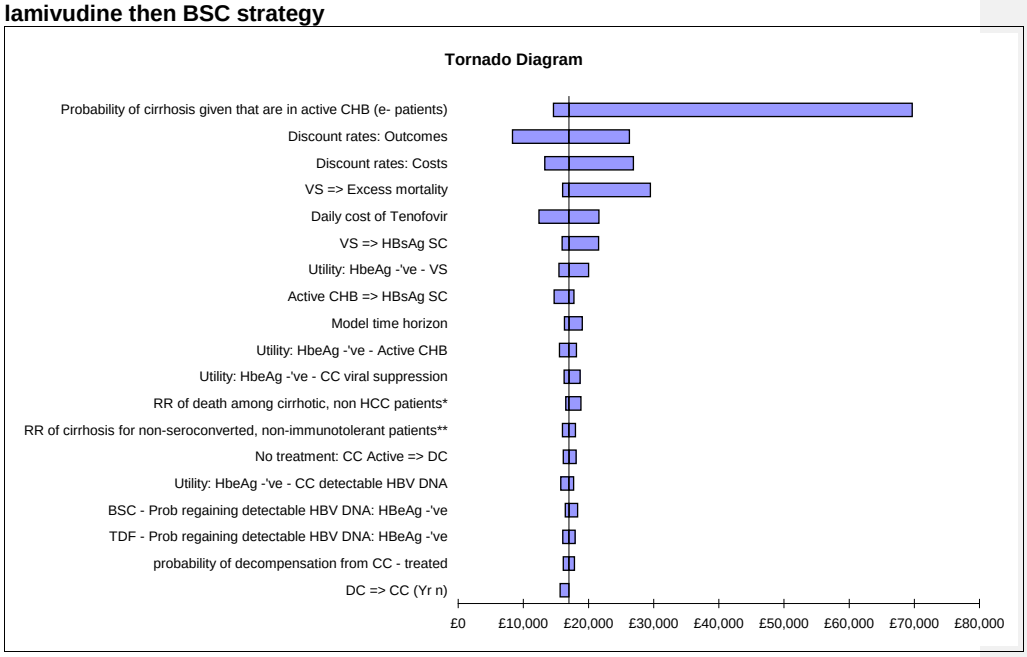
The results for the ERG's sensitivity analysis for first-line tenofovir (alone), relative to lamivudine, for HBeAg positive patients are shown in Figure 4. The model results were most sensitive to changes in the parameter values for the probability of undergoing HBeAg seroconversion with tenofovir, the probability of progressing to cirrhosis for patients with active CHB, the discount rates, and the cost of tenofovir. The model results are generally robust to changes in input parameters and the ICER remains below £30,000 per QALY gained, for all parameters.

Figure 4 Corrected tornado diagram for impact of different variables on the cost effectiveness results for the tenofovir then BSC, relative to lamivudine then BSC in HBeAg positive patients



The results of the same analysis for HBeAg negative patients are shown in Figure 5. ICERs in the model results were most sensitive to the probability of developing cirrhosis from the active CHB state, the discount rates, and the cost of tenofovir. The model results are robust to changes in the model parameters and the cost effectiveness remains below £30,000 for all parameters except for the probability of cirrhosis.

Figure 5 Corrected tornado diagram for the impact of different variables on the cost effectiveness results for HBeAg negative patients for the tenofovir then BSC versus lamivudine then BSC strategy



* Relative risk of death among cirrhotic, non HCC patients with undetectable HBV DNA (<300 copies/ml) vs those with detectable HBV DNA - untreated patients

** Relative risk of cirrhosis for non-seroconverted, non-immunotolerant patients who have undetectable (rather than detectable) HBV DNA (<300c/ml)n - untreated patients

4.3.4.3 Scenario Analysis

The MS presents scenario analyses for other key parameters and assumptions. These include discount rates, time horizon, resource use, costs, utilities, transition probabilities, resistance rates and patterns of care. The analyses also investigated the inclusion of different stopping rules. The scenario analyses are presented in tables (MS Table 45 for a cohort of HBeAg positive patients and MS Table 47 for a cohort of HBeAg negative patients) which report ICERs for the tenofovir then lamivudine strategy relative to three alternative strategies (best supportive care, lamivudine then best supportive care, or lamivudine then tenofovir) and for the lamivudine then tenofovir strategy relative to one alternative strategy (lamivudine then best supportive care). In the scenario analyses, only the time horizon significantly affected the model results, in terms of cost effectiveness.

The results presented showed that no scenario analysis (other than for reducing the time horizon) increased the ICER for first line tenofovir, in HBeAg positive patients, above £12,000 per QALY gained. The results were similar when testing the same scenarios for HBeAg negative patients.

4.3.4.4 ERG scenario analysis

The ERG re-ran the scenario analyses reported in Table 45 and Table 47 of the MS using the corrected model. The results of the scenario analyses are reported in Table 33 for HBeAg positive patients and in Table 34 for HBeAg negative patients. These broadly confirm the findings of the scenario analyses presented in the MS – that the cost effectiveness estimates are largely robust to the scenarios adopted, other than reducing the model time horizon.

Table 33 shows that applying zero discount rates improves the cost effectiveness of the lamivudine then tenofovir strategy (relative to lamivudine then BSC) and of the tenofovir then lamivudine strategy relative to all three alternative strategies. The greatest change in ICER values is associated with applying differential discount rates (6% for costs and 1.5% for benefits in this case). It should be borne in mind that these were the discount rates that applied when the pegylated interferon alfa-2a and adefovir TAR for NICE was conducted. [32]

When applying utility values derived using the standard gamble with respondents who were not chronically infected with HBV,[33] gives slightly poorer cost effectiveness estimates, though these remain below £20,000 per QALY for the comparisons included in Table 33.

Both Table 45 in the MS and Table 33, below, indicate that alternative (albeit still comparatively low) resistance rates for tenofovir have very little impact on the cost effectiveness estimates for the comparisons included in the tables. The results also appear to be robust to alternative assumptions regarding the speed at which resistance is detected. However this analysis does not appear to take account of the increased risk of flares and potentially catastrophic decompensation that may be associated with slow detection of virological resistance.

Table 33 Scenario analyses for HBeAg positive patients, using corrected model (replicates Table 45 in MS). ICERs reported as £ per QALY gained

Scenario	ICER for LAM then TDF relative to:	ICER for TDF then LAM relative to:		
	LAM then BSC	BSC	LAM then BSC	LAM then TDF
Base case	10,389	12,019	12,978	17,589
Discounting				
No discounting	9,002	9,125	9,961	11,807
Costs discounted at 6%, benefits at 1.5%	5,177	7,152	7,338	11,375
Time horizon				
5 years	48,402	54,392	65,801	76,674
10 years	20,270	25,929	29,804	40,372
20 years	12,709	15,529	17,302	24,475
30 years	11,112	13,040	14,252	19,677
40 years	10,388	12,019	12,978	17,589
50 years	10,010	11,524	12,364	16,576
60 years	9,805	11,269	12,052	16,064
Resource use				
Cost of LAM based on HIV cost	10,374	12,017	13,267	18,417
Assuming that treated patients have 11 secondary care consultations per year as assumed by SHTAC [32]	12,169	14,486	13,845	16,827
Assuming that untreated patients have the same frequency and cost of monitoring as treated patients	10,203	11,758	12,853	17,571
Increasing all disease management costs by 25%	10,378	11,843	12,845	17,236
Decreasing all disease management costs by 25%	10,398	12,195	13,112	17,942
Applying the cost of antiviral therapy for 6 months after HBeAg seroconversion	10,390	12,037	12,996	17,635
Ceasing the cost of antiviral therapy as soon as patients undergo HBeAg seroconversion	10,234	10,382	11,340	13,309
Utilities				
Alternative 1: using mild hepatitis C study[35] utilities for severe states	10,647	12,316	13,183	17,589
Alternative 2: using utilities used in the SMC submission for adefovir	9,198	10,571	11,294	14,850
Alternative 3: assuming that mild states are based on utility decrement from full health based on Wong estimates [42]	10,986	12,820	13,723	18,595
Alternative 4: based on SG utilities from non-infected patients [33]	11,492	13,725	14,447	19,797
Alternative 5: based on VAS preferences values from infected patients [33]	9,134	10,405	11,323	15,138

Scenario	ICER for LAM then TDF relative to:	ICER for TDF then LAM relative to:		
	LAM then BSC	BSC	LAM then BSC	LAM then TDF
Alternative 6: based on SG utilities from infected patients for their current disease state [33]	10,996	12,837	13,735	18,606
Transition probabilities				
Assuming that 5% of treated HBV DNA-negative cirrhotic patients show regression of cirrhosis and move back to viral suppression each year	9,914	11,560	12,387	16,765
Assuming that no decompensated patients revert to compensated cirrhosis	10,528	12,020	12,981	17,298
Assuming that the probability of moving from decompensated cirrhosis to compensated cirrhosis in the second or subsequent years of therapy is 10% of the chance in Year 1.	10,141	11,901	12,836	17,677
Assume that combination therapy is 5% more effective than monotherapy	10,388	12,019	12,978	17,589
Assuming that treatment reduces the mortality associated with HCC by 10%	10,593	12,151	13,105	17,620
Assuming that treatment reduces the mortality associated with DC by 10%	10,424	12,034	12,997	17,584
Assuming that all treatments increase the chance of HBsAg seroconversion by 50%	9,603	11,487	12,418	17,341
Assume that the probability of liver transplant is 5-fold higher than the base case	10,229	11,905	12,917	17,801
Assuming that no patients will undergo a liver transplant	10,446	12,058	13,007	17,526
Resistance				
Tenofovir resistance rates assumed to be same as those for adefovir	9,950	11,705	12,654	17,645
Tenofovir resistance rates assumed to be same as those for entecavir	8,731	11,943	12,896	16,654
Resistance rate associated with tenofovir doubles each year: 0.23%, 0.46%, 0.93%, 1.85% and 3.0% in years 1-4 and Year 5/n, respectively.	9,015	11,659	12,573	17,605
Patterns of care				
Assuming that resistance is picked up as soon as HBV DNA levels rise/become detectable	10,277	12,015	12,877	17,574
Assuming that resistance is picked up 3 months after HBV DNA levels rise/become detectable	10,498	12,023	13,079	17,614
Assuming that resistance is picked up 6 months after HBV DNA levels rise/become detectable	10,708	12,033	13,281	17,700
Assuming that resistance is picked up 12 months after HBV DNA levels rise/become detectable	11,090	12,054	13,687	18,022

Scenario	ICER for LAM then TDF relative to:	ICER for TDF then LAM relative to:		
	LAM then BSC	BSC	LAM then BSC	LAM then TDF
Assuming pts in the CC, DC, post-LT, LT or HCC states do not receive antivirals AND all patients assumed to have active CHB at baseline	12,435	13,612	15,352	20,234
Assuming pts in the CC state receive antivirals but those in DC, HCC, LT or post-LT states do not	10,273	12,032	12,819	17,341
Assuming pts with HCC do not receive antivirals, but those in the DC, LT, post-LT states do	10,379	12,019	12,971	17,584
Assuming that pts in the DC, LT, post-LT states do not receive antivirals but those with HCC do	10,293	12,032	12,827	17,334
Assuming pts in the CC, DC, post-LT, LT or HCC states do not receive antivirals AND all patients assumed to have active CHB at baseline	12,435	13,612	15,352	20,234

The results of the scenario analyses for HBeAg negative patients (see Table 34) are very similar to those for HBeAg positive patients, in that the cost effectiveness estimates are generally robust to the scenarios tested, with the exception of reducing the model time horizon. As with the HBeAg positive cohort, zero discount rates are associated with lower ICERs than for the base case while adopting differential rates for costs and benefits give the most favourable estimates.

In contrast with the HBeAg positive cohort, applying the utility values derived by Ossa and colleagues[33] from uninfected respondents gives slightly more favourable ICERs. As with the HBeAg positive cohort varying the resistance rate for tenofovir has little impact on the ICER. As HBeAg negative patients cannot undergo HBeAg seroconversion, there is no identified stopping rule for this group of patients (other than HBsAg seroconversion). Hence treatment duration may extend for the patients lifetime and, in that context, it may be surprising how little impact the resistance rates have on the cost effectiveness estimates.

Table 34 Scenario analyses for HBeAg negative patients, using corrected model (replicates Table 47 in MS). ICERs reported as £ per QALY gained

Scenario	ICER for LAM then TDF relative to:	ICER for TDF then LAM relative to:		
	LAM then BSC	BSC	LAM then BSC	LAM then TDF
Base case	18,547	17,640	16,984	14,549

Scenario	ICER for LAM then TDF relative to:	ICER for TDF then LAM relative to:		
	LAM then BSC	BSC	LAM then BSC	LAM then TDF
Discounting				
No discounting	15,043	13,621	13,166	10,204
Costs discounted at 6%, benefits at 1.5%	9,321	9,692	8,974	8,429
Time horizon				
5 years	185,859	124,646	150,846	134,266
10 years	56,787	47,280	51,897	46,777
20 years	25,834	24,096	24,037	21,294
30 years	20,276	19,278	18,714	16,232
40 years	18,547	17,640	16,984	14,549
50 years	17,885	16,969	16,293	13,866
60 years	17,599	16,664	15,984	13,559
Resource use				
Cost of LAM based on HIV cost	18,547	17,637	17,161	15,001
Assuming that treated patients have 11 secondary care consultations per year as assumed by SHTAC [32]	20,713	20,398	18,631	15,387
Assuming that untreated patients have the same frequency and cost of monitoring as treated patients	18,393	17,449	16,881	14,525
Increasing all disease management costs by 25%	19,023	17,852	17,159	14,255
Decreasing all disease management costs by 25%	18,072	17,428	16,809	14,842
Utilities				
Alternative 1: using mild hepatitis C study[35] utilities for severe states	20,178	18,222	17,477	13,806
Alternative 2: using utilities used in the SMC submission for adefovir	18,163	15,854	15,180	11,446
Alternative 3: assuming that mild states are based on utility decrement from full health based on Wong estimates [42]	18,571	17,672	17,016	14,588
Alternative 4: based on SG utilities from non-infected patients [33]	17,089	16,598	15,998	14,197
Alternative 5: based on VAS preferences values from infected patients [33]	17,746	16,437	15,811	12,995
Alternative 6: based on SG utilities from infected patients for their current disease state [33]	18,547	17,640	16,984	14,549
Transition probabilities				
Assuming that 5% of treated HBV DNA-negative cirrhotic patients show regression of cirrhosis and move back to viral suppression each year	16,031	15,812	15,041	13,404
Assuming that no decompensated patients revert to compensated cirrhosis	18,655	17,643	16,988	14,401

Scenario	ICER for LAM then TDF relative to:	ICER for TDF then LAM relative to:		
	LAM then BSC	BSC	LAM then BSC	LAM then TDF
Assuming that the probability of moving from decompensated cirrhosis to compensated cirrhosis in the second or subsequent years of therapy is 10% of the chance in Year 1.	18,162	17,415	16,754	14,546
Assume that combination therapy is 5% more effective than monotherapy	18,547	17,640	16,984	14,549
Assuming that treatment reduces the mortality associated with HCC by 10%	18,682	17,734	17,081	14,562
Assuming that treatment reduces the mortality associated with DC by 10%	18,589	17,665	17,012	14,549
Assuming that all treatments increase the chance of HBsAg seroconversion by 50%	18,054	17,042	16,438	13,973
Assume that the probability of liver transplant is 5-fold higher than the base case	18,249	17,490	16,834	14,566
Assuming that no patients will undergo a liver transplant	18,672	17,701	17,046	14,544
Resistance				
Tenofovir resistance rates assumed to be same as those for adefovir	18,818	18,031	17,230	14,272
Tenofovir resistance rates assumed to be same as those for entecavir	20,926	17,677	16,993	15,378
Resistance rate associated with tenofovir doubles each year: 0.23%, 0.46%, 0.93%, 1.85% and 3.0% in years 1-4 and Year 5/n, respectively.	19,440	17,840	17,048	14,895
Patterns of care				
Assuming that resistance is picked up as soon as HBV DNA levels rise/become detectable	18,454	17,633	17,043	14,799
Assuming that resistance is picked up 3 months after HBV DNA levels rise/become detectable	18,641	17,647	16,926	14,307
Assuming that resistance is picked up 6 months after HBV DNA levels rise/become detectable	18,830	17,662	16,815	13,848
Assuming that resistance is picked up 12 months after HBV DNA levels rise/become detectable	19,208	17,692	16,612	13,024
Assuming pts in the CC, DC, post-LT, LT or HCC states do not receive antivirals AND all patients assumed to have active CHB at baseline	18,851	17,748	17,814	16,259
Assuming pts in the CC state receive antivirals but those in DC, HCC, LT or post-LT states do not	18,605	17,663	16,896	14,199
Assuming pts with HCC do not receive antivirals, but those in the DC, LT, post-LT states do	18,547	17,641	16,982	14,544
Assuming that pts in the DC, LT, post-LT states do not receive antivirals but those with HCC do	18,608	17,663	16,898	14,200

Scenario	ICER for LAM then TDF relative to:	ICER for TDF then LAM relative to:		
	LAM then BSC	BSC	LAM then BSC	LAM then TDF
Assuming pts in the CC, DC, post-LT, LT or HCC states do not receive antivirals AND all patients assumed to have active CHB at baseline	18,851	17,748	17,814	16,259

4.3.4.5 Probabilistic Sensitivity Analysis

The PSA can be run by clicking on the 'Simulation' button in the 'Simulations' worksheet of the Excel model. The PSA takes about 9 hours to run on a 2.8 MHz computer for 20 scenarios for 2000 simulations each. The PSA included only those scenarios lying closest to the cost-effectiveness frontier and other scenarios are unlikely to have any effect on the probability that first line tenofovir is cost-effective.

The MS stated that the results presented in the PSA confirmed those of the base-case analyses, demonstrating that first line use of tenofovir is the most cost-effective strategy for a cost-effective threshold of £20,000 - £30,000 per QALY gained. As discussed in section 4.3.3.1, there were a number of errors in the presentation of the PSA in the MS. The ERG requested clarification from the manufacturer regarding these errors and the manufacturer's response is included as an Appendix to this report. A brief summary of the amended PSA results is provided below.

HBeAg positive patients

Figure 12 in the Appendix to this document presents cost-effectiveness acceptability curves derived from the manufacturer's amended PSA for patients with HBeAg positive CHB, including the cost-effectiveness acceptability frontier (CEAF) (which shows portions of the CEAC for interventions deemed optimal, using the maximum net benefit criterion, over a range of willingness to pay values). The four strategies that are optimal using this criterion, at some willingness to pay values over the range from zero to £50,000 per QALY gained, are:

- BSC (£0 to £6,500)
- Lamivudine then BSC (£7,000 to £10,500)
- Tenofovir then lamivudine (£11,000 to £28,000)
- Tenofovir then tenofovir plus lamivudine (£28,000 to £50,000).

The willingness to pay ranges are not reported in the manufacturer's amended analyses – these have been estimated from the CEAF in Figure 12 in the Appendix.

Table 35 below shows the probability of strategies, identified from the CEF in the deterministic analysis of the model, being cost-effective at a range of threshold values of willingness to pay per QALY gained.

Table 35 Probability interventions are cost effective at varying thresholds of willingness to pay per QALY gained, for HBeAg positive patients – from manufacturer's amended PSA

Treatment strategy	Probability of being cost effective at given willingness to pay threshold		
	£20,000	£30,000	£50,000
BSC	6.55%	2.75%	1.05%
Lamivudine then BSC	2.05%	0.65%	0.05%
Lamivudine then tenofovir	21.00%	11.85%	4.65%
Tenofovir then lamivudine	35.90%	27.60%	18.40%
Tenofovir then tenofovir plus lamivudine	20.40%	33.10%	34.25%
Tenofovir then tenofovir plus lamivudine then entecavir	3.30%	10.00%	21.95%

The amended analysis presented by the manufacturer did not include total cost and total QALY estimates for each strategy. Hence the ERG was not able to conduct a probabilistic replication of Table 36 of the MS (base case results from the deterministic analysis of the model, summarised in Table 17 of this report) from the manufacturer's amended PSA. The ERG re-ran the probabilistic analysis, using the submitted electronic model, after making the changes described in section 4.3.3.1 to enable the PSA to be run for a cohort of HBeAg positive patients. Table 36 reports the mean cost and QALY estimates from the re-run PSA and ICERs estimated for treatment strategies along the cost effectiveness frontier.

Table 36 Mean cost and mean QALYs and cost effectiveness estimates from the PSA for HBeAg positive patients

Treatment strategy	Mean QALY per patient	Mean cost per patient (£)	ICER (£ per QALY gained)
BSC	16.64	9,500	
Lamivudine then BSC	17.19	13,098	6,517
Lamivudine then tenofovir	18.14	25,125	
Tenofovir then lamivudine	18.98	31,886	10,473
Tenofovir then tenofovir plus lamivudine	19.00	32,301	25,695
Tenofovir then tenofovir plus lamivudine then entecavir	19.00	32,303	238,359

As suggested in the MS, this analysis broadly confirms the deterministic analysis, in terms of the selection of treatment strategies on the cost effectiveness frontier. However, the ICERs, derived using the mean values from the PSA, are substantially less favourable for the majority of the sequential treatment strategies. Note that in this analysis, unlike the deterministic analysis of the model, lamivudine then tenofovir is no longer on the CEF – it is excluded by extended dominance, with an ICER relative to lamivudine then BSC of £12,574 per QALY gained – while the ICER for tenofovir then tenofovir plus lamivudine has approximately doubled.

HBeAg negative patients

Figure 15 in the Appendix to this document presents CEACs derived from the manufacturer's amended PSA for patients with HBeAg negative disease, including the CEAF. The four strategies that are optimal using the maximum net benefit criterion over the range from zero to £50,000 per QALY gained, are:

- BSC (£0 to £10,500)
- tenofovir then lamivudine (£11,500 to £16,500)
- tenofovir then tenofovir plus lamivudine (£16,500 to £26,500)
- tenofovir then tenofovir plus lamivudine then entecavir (£27,500 to £50,000).

The willingness to pay ranges are not reported in the manufacturer's amended analyses – these have been estimated from the CEAF in Figure 15 in the Appendix.

Table 37 below shows the probability of strategies, identified from the cost effectiveness frontier in the deterministic analysis of the model, being cost effective at a range of threshold values of willingness to pay per QALY gained.

Table 37 Probability interventions are cost effective at varying thresholds of willingness to pay per QALY gained, for HBeAg negative patients – from manufacturer's amended PSA

Treatment strategy	Probability of being cost effective at given willingness to pay threshold		
	£20,000	£30,000	£50,000
BSC	6.95%	2.00%	0.65%
Tenofovir then lamivudine	17.80%	4.50%	1.20%
Tenofovir then tenofovir plus lamivudine	44.70%	37.60%	23.10%
Tenofovir then tenofovir plus lamivudine then entecavir	26.55%	52.90%	72.65%

The ERG re-ran the probabilistic analysis, using the submitted electronic model, for a cohort of HBeAg negative patients. Table 38 reports the total cost and QALY estimates from the re-run PSA and ICERs estimated for treatment strategies along the cost effectiveness frontier.

Table 38 Mean cost and mean QALYs and cost effectiveness estimates from the PSA for HBeAg negative patients

Treatment strategy	Mean QALY per patient	Mean cost per patient (£)	ICER (£ per QALY gained)
BSC	12.21	13,944	
Tenofovir then lamivudine	16.19	59,417	11,425
Tenofovir then tenofovir plus lamivudine	16.27	60,734	16,081
Tenofovir then tenofovir plus lamivudine then entecavir	16.27	60,739	26,616

As suggested in the MS, this analysis broadly confirms the deterministic analysis, in terms of the selection of treatment strategies on the cost effectiveness frontier. While the ICERs, derived using the mean values from the PSA, are less favourable than for the deterministic analysis reported in Table 18, the differences between the deterministic and probabilistic analysis is not as great as for the HBeAg positive cohort.

Probability distributions and sampling in the PSA

The MS includes all parameters in the model in the PSA and these vary according to the ranges chosen for the sensitivity analyses. The MS does not include any description or justification of the distributions used for the PSA. The ERG has reviewed the distributions used in the Excel model and these generally appear appropriate. The model typically uses the beta distribution for utilities and transition probabilities and the gamma distribution for costs.

The ERG identified what appear to be errors in the parameterisation of distributions applied to relative risks in the PSA for this model. No account appears to have been taken of the fact that standard errors and CIs for relative risks are calculated using the log scale. For example, when deriving relative risks of death for cirrhotic patients with viral suppression, compared to those with detectable virus, the MS reports using the relative risk and 95% CIs from a study by Fattovich and colleagues[30]. The published values of 5.90 for the relative risk, with a 95% confidence interval of 1.64 to 21.30, were for HBV DNA positive patients, compared with those who were HBV DNA negative – hence the reciprocals of these values (1/5.90 = 0.1695, 1/1.64 = 0.6098 and 1/21.30 = 0.0469) were used. However, the standard error for the relative risk was estimated, in the model, by assuming that this can be recovered directly from the reported 95% CI as:

$$\frac{\text{UCI} - \text{LCI}}{2*1.9600} = \frac{0.6098 - 0.0469}{2*1.9600} = 0.1436$$

(where UCI indicates the upper limit of the confidence interval and LCI the lower limit. This formula applies to a 95% CI).

This approach takes no account of the use of the log scale for estimating the 95% CI for a relative risk. The calculation below can be used to correctly recover the standard error of the log of the relative risk from the 95% CI:

$$\frac{\ln(\text{UCI}) - \ln(\text{LCI})}{2*1.9600} = \frac{-0.4947 - -3.0587}{2*1.9600} = 0.6541$$

(where ln(UCI) indicates the natural log of the upper limit of the confidence interval and ln(LCI) the natural log of the lower limit. This formula is correct to recover the standard error from a 95% confidence interval).

Given that this method derives a standard error for the log relative risk, it may be most appropriate to sample from a normal distribution, with mean equal to the log of the reported point estimate for the relative risk (1.7750) and standard deviation equal to the standard error of the log relative risk (0.6541). To derive the relative risk, for use in the model, the sampled value needs to be exponentiated. It should be noted that the mean relative risk estimated in this way (i.e. the mean of the exponentiated sampled values) will not be equal to the original point estimate for the relative risk.[50] It appears that standard errors for all relative risks in the model were estimated incorrectly.

In addition, a number of sampling distributions used in the submitted electronic model return error values in the PSA. The spreadsheet has been set up so that, where a distribution returns an error it is replaced by the point estimate from the deterministic base case, for the relevant model input parameter. This is the case for a number of the relative risk parameters and also for the parameter estimating the number of months between the development of virologic resistance and patients changing treatment. The effect of using the mean, rather than sampled values for these parameters, is that the reported PSA may underestimate uncertainty in the model. The ERG corrected the errors in parameterisation for these distributions and re-ran the PSA, see section 4.3.4.6 below.

4.3.4.6 ERG Probabilistic Sensitivity Analysis

The ERG re-ran the probabilistic sensitivity analyses for the corrected model. In addition to the corrections applied in the deterministic model (i.e. correcting discounting of QALYs, double application of the reduction of excess mortality for patients with compensated cirrhosis who achieve viral suppression, and construction of transition matrices and all-cause mortality rates) the corrections to the parameterisation of distributions for relative risks and for time between development of virologic resistance and patients' changing treatment, described above, were applied. The model still returned a number of simulations with no real values for total costs and QALYs for some treatment strategies (6.5% for the HBeAg positive cohort and 8% for the HBeAg negative cohort).

HBeAg positive patients

Figure 6 illustrates the CEACs and CEAF derived from the ERG's PSA for patients with HBeAg positive CHB. The CEAF is shown by the bold lines in Figure 6, with labels for strategies on the frontier. Note that the CEAF is discontinuous and does not necessarily identify strategies with the greatest probability of being cost-effective at a given willingness to pay threshold. The four strategies that are optimal using the maximum net benefit criterion, over the range from zero to £100,000 per QALY gained, are:

- BSC (£0 to £11,000)
- lamivudine then BSC (£12,000 to £18,000)
- tenofovir then lamivudine (£19,000 to £60,000)
- tenofovir then tenofovir plus lamivudine (£60,000 to £100,000).

Figure 6 Cost-effectiveness acceptability curves and Cost-effectiveness acceptability frontier from ERG PSA HBeAg positive patients

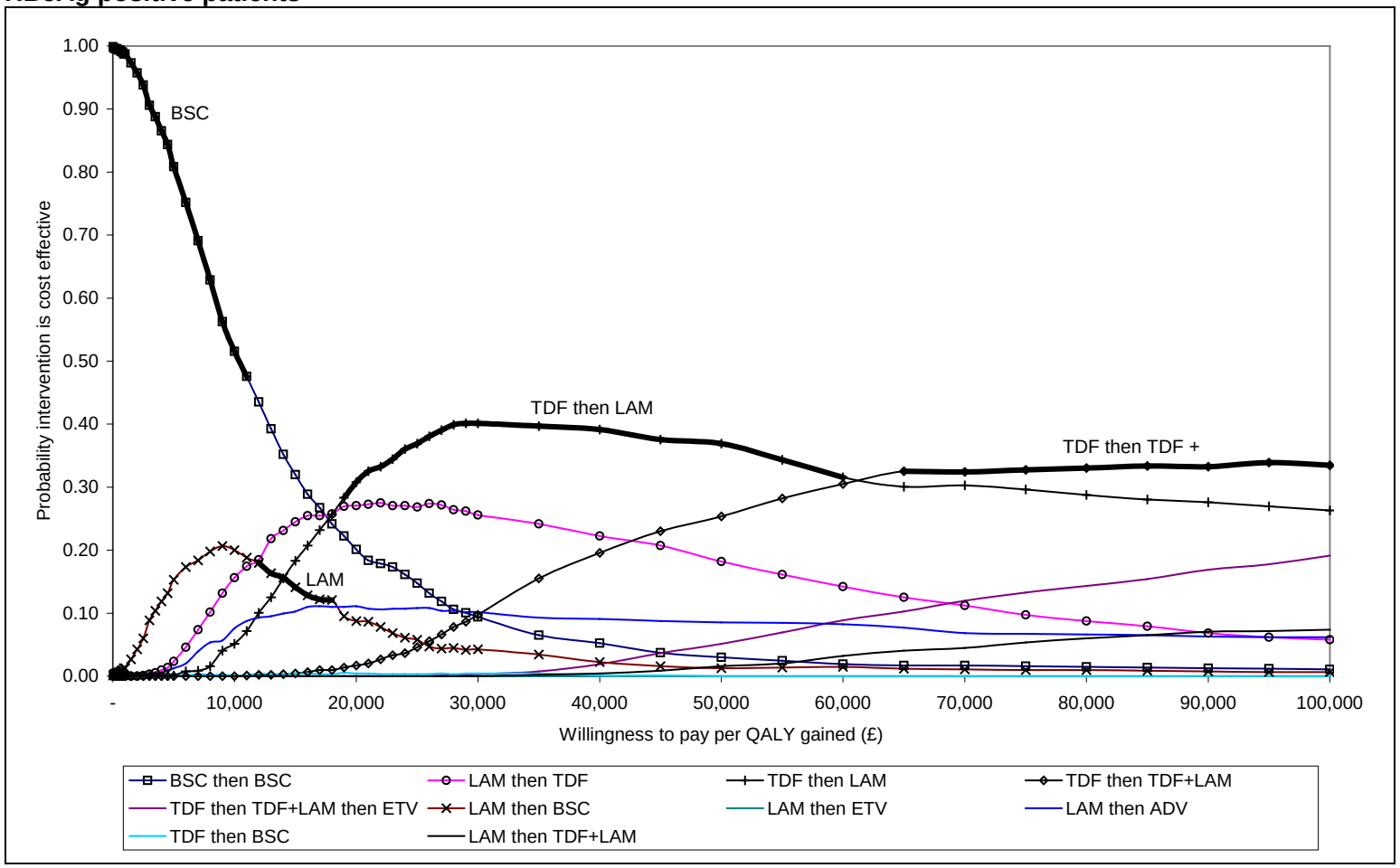


Table 39 below shows the probability of strategies, identified from the cost effectiveness frontier in the deterministic analysis of the model, being cost effective at a range of threshold values of willingness to pay per QALY gained.

Table 39 Probability interventions are cost effective at varying thresholds of willingness to pay per QALY gained, for HBeAg positive patients – from ERG PSA

Treatment strategy	Probability of being cost effective at given willingness to pay threshold		
	£20,000	£30,000	£50,000
BSC	20.1%	9.4%	3.0%
Lamivudine then BSC	8.8%	4.3%	1.3%
Lamivudine then tenofovir	27.1%	25.6%	18.2%
Tenofovir then lamivudine	30.8%	40.1%	36.9%
Tenofovir then tenofovir plus lamivudine	1.7%	9.7%	25.3%
Tenofovir then tenofovir plus lamivudine then entecavir	0.0%	0.3%	5.1%

Table 40 reports the mean cost and QALY estimates from the re-run PSA and ICERs estimated for treatment strategies along the cost effectiveness frontier.

Table 40 Mean cost, mean QALYs and cost effectiveness estimates for HBeAg positive patients - from ERG PSA

Treatment strategy	Mean QALY per patient	Mean cost per patient (£)	ICER (£ per QALY gained)
BSC	10.65	8,201	
Lamivudine then BSC	10.95	11,597	11,172
Lamivudine then tenofovir	11.38	21,175	
Tenofovir then lamivudine	11.80	27,377	18,722
Tenofovir then tenofovir plus lamivudine	11.80	27,684	60,302
Tenofovir then tenofovir plus lamivudine then entecavir	11.80	27,686	Dominated

As with the comparison between the deterministic and manufacturer's amended probabilistic results, the incremental cost effectiveness ratios, derived using the mean values from the PSA, are substantially less favourable for the majority of the sequential treatment strategies. Once

again, in the probabilistic analysis lamivudine then tenofovir is no longer on the cost effectiveness frontier – it is excluded by extended dominance, with an ICER relative to lamivudine then BSC of £22,715 per QALY gained – while the ICER for tenofovir then tenofovir plus lamivudine has more than doubled.

HBeAg negative patients

Figure 7 reports the cost effectiveness acceptability curves and cost effectiveness acceptability frontier derived from the ERG's probabilistic sensitivity analysis for patients with HBeAg negative disease. The four strategies that are optimal using the maximum net benefit criterion, at some willingness to pay values over the range from zero to £100,000 per QALY gained, are:

- BSC (£0 to £19,000 per QALY gained)
- tenofovir then lamivudine (£20,000 to £30,000 per QALY gained)
- tenofovir then tenofovir plus lamivudine (£35,000 to £50,000)
- tenofovir then tenofovir plus lamivudine then entecavir (£55,000 to £100,000).

Figure 7 Cost effectiveness acceptability curves and cost effectiveness acceptability frontier from ERG PSA – HBeAg negative patients

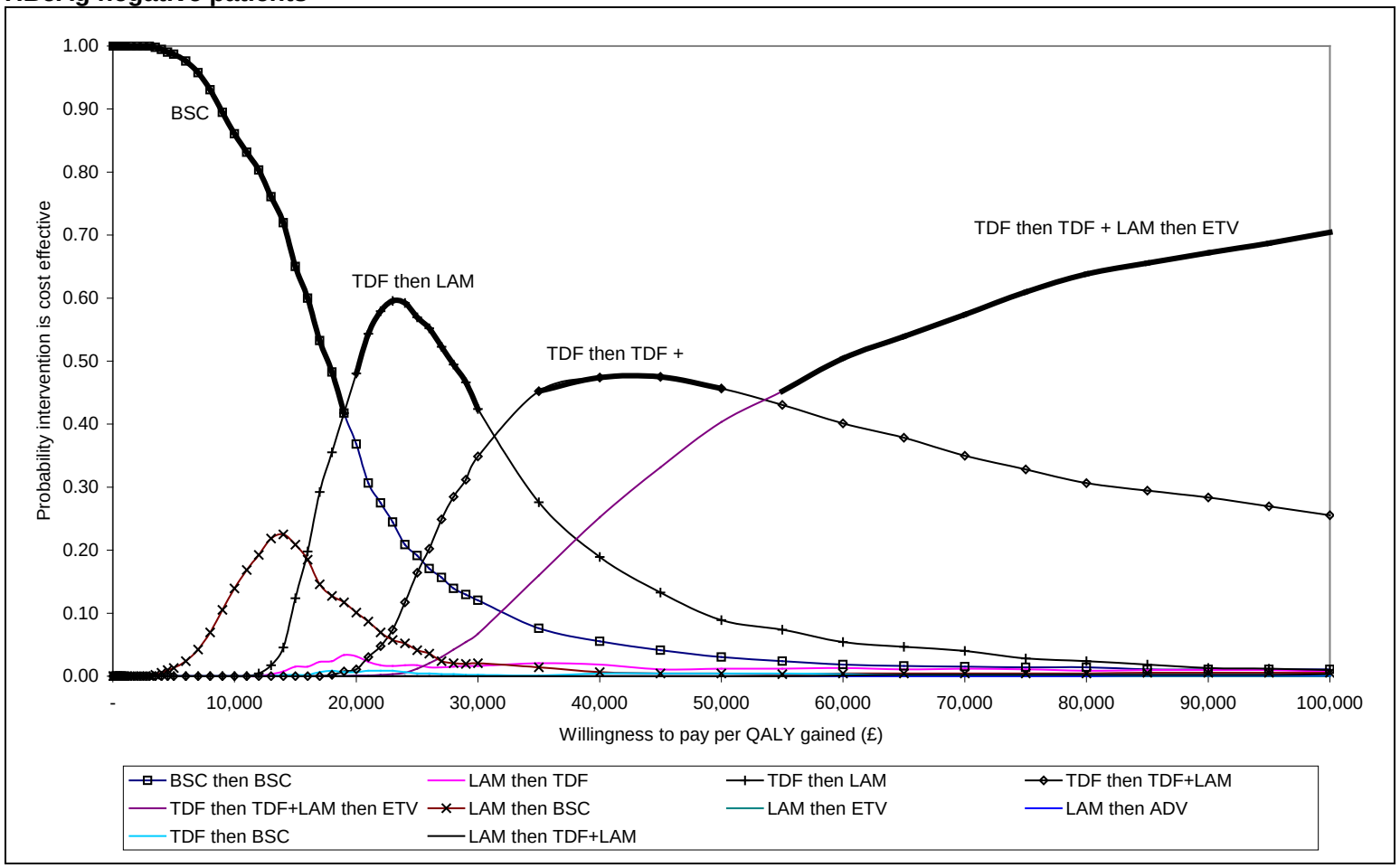


Table 41 below shows the probability of strategies, identified from the cost effectiveness frontier in the deterministic analysis of the model, being cost effective at a range of threshold values of willingness to pay per QALY gained.

Table 41 Probability interventions are cost effective at varying thresholds of willingness to pay per QALY gained, for HBeAg negative patients – from ERG PSA

Treatment strategy	Probability of being cost effective at given willingness to pay threshold		
	£20,000	£30,000	£50,000
BSC	36.8%	12.1%	3.0%
Tenofovir then lamivudine	48.0%	42.4%	8.9%
Tenofovir then tenofovir plus lamivudine	1.1%	34.9%	45.7%
Tenofovir then tenofovir plus lamivudine then entecavir	0.1%	6.7%	40.3%

Table 42 reports the mean cost and QALY estimates from the re-run PSA and ICERs estimated for treatment strategies along the cost effectiveness frontier.

Table 42 Mean cost, mean QALYs and cost effectiveness estimates for HBeAg negative patients – from ERG PSA

Treatment strategy	Mean QALY per patient	Mean cost per patient (£)	ICER (£ per QALY gained)
BSC	8.39	12,220	
Tenofovir then lamivudine	10.30	49,461	19,443
Tenofovir then tenofovir plus lamivudine	10.33	50,423	32,709
Tenofovir then tenofovir plus lamivudine then entecavir	10.33	50,430	51,595

As with the cohort of patients with HBeAg positive CHB the incremental cost effectiveness ratios, derived using the mean values from the PSA, are less favourable than in the deterministic analysis. However the difference between the ICERs calculated in the deterministic and probabilistic analyses are less marked for the cohort of HBeAg negative patients.

4.3.5 Comment on validity of results presented with reference to methodology used

The structure adopted for the economic model is reasonable, and consistent with previous economic evaluations. The model has been appropriately structured to incorporate resistance to anti-viral agents, and to retain memory of the agents that patients are resistant to. The incorporation of a transition from HBeAg positive to HBeAg negative CHB (for patients in the HBeAg seroconverted state) is novel. This accords with current understanding of the natural history of CHB and was regarded as a reasonable approach by the clinical advisors to the ERG.

Methods used to derive input data for the economic model are generally appropriate. The use of an MTC for estimating the effectiveness of anti-viral agents (in terms of viral suppression and HBeAg seroconversion) is reasonable and the analysis appears to have been conducted appropriately. The pooled analysis for estimating resistance to anti-viral agents also appears reasonable, but was severely hampered by sparsity of data. However, overall the reporting of the analyses is poor, particularly in terms of searching for and critical appraisal of studies used to estimate parameter inputs. In many cases very limited information is provided on studies contributing data to key input parameters in the model. For example, it is not clear which six studies were used to estimate the ratios used to determine viral suppression and HBeAg seroconversion in the second year of treatment. There was no evidence of systematic searches for data to estimate parameters and no critical appraisal of the scope, quality or appropriateness of the data.

The methods of analysis are generally appropriate and conform with NICE methodological guidelines. However a number of errors were detected in the submission – transcription errors in the MS and analytical errors in the electronic model. These have been documented in this report along with corrected results, where this is possible. In all cases the ERG has attempted to estimate the extent to which such errors may have systematically biased the results presented in the MS and have concentrated on those errors or uncertainties which may appear most likely

to have introduced bias. As far as we have been able to check the input data in the model are generally in accordance with those listed in the MS and appendices. Notwithstanding this, we cannot guarantee that there are no remaining errors in the MS or the model.

4.3.6 Summary of uncertainties and issues

- The ERG identified a serious error in the electronic model in the way that QALY outcomes were discounted. This applies to both the deterministic (base case and sensitivity/scenario analyses) and the probabilistic analyses. Correcting this error lead to less favourable ICERs for anti-viral treatments.
- Pre-model analysis of key input parameters to the model was hampered by sparsity of data:
  - Stable results could not be estimated for the HBeAg negative patient cohort in the MTC;
  - Effectiveness parameters included in the MTC were only estimated for one year of treatment – this contrasts with the expectation of long-term (possibly lifetime) treatment with nucleoside/ nucleotide analogues;
  - Limited data on resistance was available for some key anti-viral agents;
  - The influence of viral load on risk of disease progression has only relatively recently been established. As a result there are limited long term and natural history studies reporting outcomes by viral load.

  However, the model has tended to use measures of uncertainty for input parameters that are based on statistical analyses (for example, standard deviations or standard errors) which will not reflect the true degree of uncertainty in estimating these parameters.
- There is a need to consider the impact of resistance on cost-effectiveness. Adopting anti-viral agents with better resistance profiles is likely to improve outcomes. However this is achieved at greater cost – since treatment duration will be longer, all other things being equal. This is particularly a problem for combination treatments (adopted with the aim of reducing resistance) since the additional cost of the combination is absorbed for treatment initiation, while the benefits (in terms of reduced or averted drug resistance) will not be fully realised until some time in the future.
- Adopting the same starting age for HBeAg positive and HBeAg negative patient cohorts may be open to question. The MS has justified this on the basis of data from an audit of

patients at a UK liver centre. However, the total sample in the audit was only 85 patients. The natural history implied by the structure of the model used in this evaluation suggests that HBeAg negative patients should be older, on average, than HBeAg positive patients (given that HBeAg negative CHB emerges in a proportion of patients reactivating disease from the HBeAg seroconverted state). This is in accordance with the clinical view that HBeAg negative CHB is a later phase of the natural history of infection.

5 Discussion

5.1 Summary of clinical-effectiveness issues

- Tenofovir is one of a growing number of treatment options for patients with CHB. The manufacturer has provided a reasonably sound assessment of its clinical-effectiveness based on two pivotal RCTs in HBeAg positive and negative nucleos(t)ide naïve patients, albeit with some limitations.
- Tenofovir was statistically significantly superior to adefovir for the primary composite outcome of HBV DNA response (400 copies/mL) and histologic response. There were also statistically significant differences between the two drugs in terms of secondary outcomes HBV DNA response (400 copies/mL) and ALT (HBeAg positive patients only). However, there were no statistically significant differences for histology and HBeAg seroconversion. Tenofovir was generally well tolerated and adverse effects were generally similar to adefovir.
- Clinical-effectiveness data beyond one year are observational and should be interpreted with caution.
- Tenofovir appears to have a favourable resistance profile based on limited data currently available. Whether this will be maintained with long-term treatment is yet to be established. These data will be important to guide decisions as to whether to initiate treatment with monotherapy or combination therapy. If resistance in the long-term is low clinicians may decide to initiate treatment with tenofovir monotherapy, thus reserving other nucleos(t)ides as future treatment options if necessary. If resistance to tenofovir monotherapy is likely to be high then a clinically plausible combination of nucleos(t)ides (e.g. lamivudine and tenofovir) may be preferable in order to suppress the selection of resistant strains. However, there is

currently a lack of RCT data for the clinical-effectiveness of tenofovir in combination with other nucleos(t)ides.

- There are a lack of head-to-head RCTs comparing tenofovir with other nucleos(t)ides, necessitating the production of an MTC. The results suggest that tenofovir has the highest probability of HBV DNA <300 copies/ML response at one year of treatment. There were no statistically significant differences between the nucleos(t)ides in terms of HBeAg seroconversion.
- The MTC is subject to certain methodological limitations, and it was not possible to conduct one for HBeAg negative nucleos(t)ide naïve patients, or lamivudine refractory patients.

5.2 Summary of cost-effectiveness issues

- The model structure and methods adopted for the economic evaluation are reasonable and are generally appropriate. The model structure is consistent with previous economic evaluations and has been appropriately structured to incorporate resistance to anti-viral agents, and maintain a history where patients have developed resistance to agents included in the treatment strategy. However, the reporting of pre-model analyses used to estimate parameter inputs is poor, with limited information on studies contributing data to key input parameters in the model, no evidence of systematic searches for data to estimate parameters and no critical appraisal of the scope, quality or appropriateness of included studies.
- A number of errors were detected in the submission, which have been documented in this report. Where possible, corrected analyses have been presented by the ERG. In all cases the ERG has attempted to estimate the extent to which such errors may have systematically biased the results presented in the MS. The ERG identified a serious error in the electronic model in the way that QALY outcomes were discounted. This applies to both the deterministic (base case and sensitivity/scenario analyses) and the probabilistic analyses.
- Pre-model analysis of key input parameters to the model was hampered by sparsity of data. The submission has tended to use measures of uncertainty for input parameters that are based on statistical analyses (for example, standard deviations or standard errors) which will not reflect the true degree of uncertainty in estimating these parameters. Once the identified errors have been corrected, and more appropriate estimates of uncertainty have been incorporated in the analysis, the ERG feels the model provides a reasonable

characterisation of the cost-effectiveness of treatment strategies containing tenofovir, in the treatment of CHB.

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~~7~~Appendix – Response from Gilead to clarification questions by the ERG

Formatted: Bullets and Numbering

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 trials.com in addition to NewDrugFile?)	These databases were not searched. However, we did search manufacturers' websites and the proceedings of a key conference (AASLD 2007) to identify ongoing trials.
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-	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.

	randomised trials reported in a total of 122 papers?	
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	We apologise, this was marked in error and the submission has been amended accordingly.

	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)?	
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	The pre-specified inclusion criteria for the meta-analysis excluded studies in which ≥50% of the total cohort were co-infected with HIV. [redacted] "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.

[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.

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

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	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.

	. 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 into 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?)	

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	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.

	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).	
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	[redacted][2]

[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.

	would support this assumption?	
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	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.

	were HBeAg negative?	
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 % annua	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.

	l 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 (femal	

	e). 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.	
B5	Pleas	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

	e clarify whether there are any assumptions (implicit or explicit) in the model, regarding regression from compensated cirrhosis to CHB/ viral suppression?	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.
B5. a	Page 116 of the MS states that patien	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.

	ts 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?	
B5.b	Please could you state whether patients who achieve HBeAg seroconversion from a compensated cirrhosis state (either compensated cirrhosis with detectable HBV DNA	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.

	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 patien	

	ts previous health state(s)?	
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	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).

	data and/ or was this assumption clinically validated?	
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	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.

	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 Hepatol 2008; 48:728-735), including up to two years of data?	
B7	The section on utilities (7.2.8.	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

	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,	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.

	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?	
B8	There appear to be inconsistencies between Table 37 and Table 38 in the submission (and between Table 37 and the submitted electr	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.

	onic 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 betw een	

	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 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	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. 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.

	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?	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.
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?	
B10	There appear to be errors in the	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.

	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	
B10.a	Please can you confirm that the calculation of mean ICER	

	s 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 spreadshee	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.

	t 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)?	
B11	When running the PSA for the submitted electronic model (which allows analysis of ten treatment strategies	Yes, we did see these notifications when conducting PSA and such simulations were excluded from all averages presented in the report.

	(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 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 show	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.

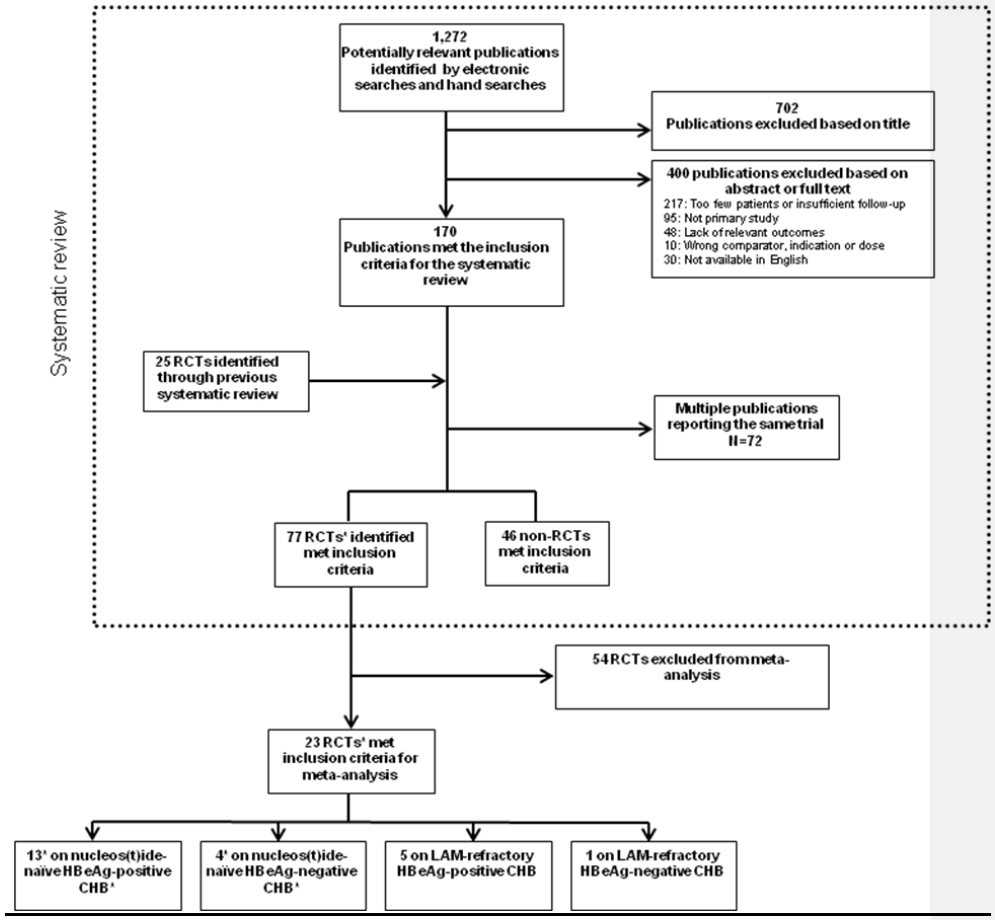
	n on each of the Excel worksheets	
B12.a	Is it possible to run the model for a smaller number of scenarios, for example only scenarios 1-20, without access to the visual basic code?	The number of scenarios considered is defined in the visual basic code (currently this is set to 20), The ERG have been 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	All deterministic results are generated on the scenarios sheet. 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.

	of the scenarios on its own deterministically and if so where are the results shown?	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	A

	Proc 2001; 33(7-8): 3643-4.	
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	B

	hepatitis B who have shown disease progression by reaching a clinical endpoint. Data on file 2005.	
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 2004; 40(4 Suppl 1): 656a-7a.	C
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.	B

	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.	
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 dipivoxil therapy in chronic hepatitis B: two placebo-controlled Phase II studies. Hepatology.1998;28(Suppl 4 Pt 2):317 A.	B
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	B

	depending on the resistance substitutions present. Antimicrob Agents Chemother 2007; 51(3): 902-11	

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

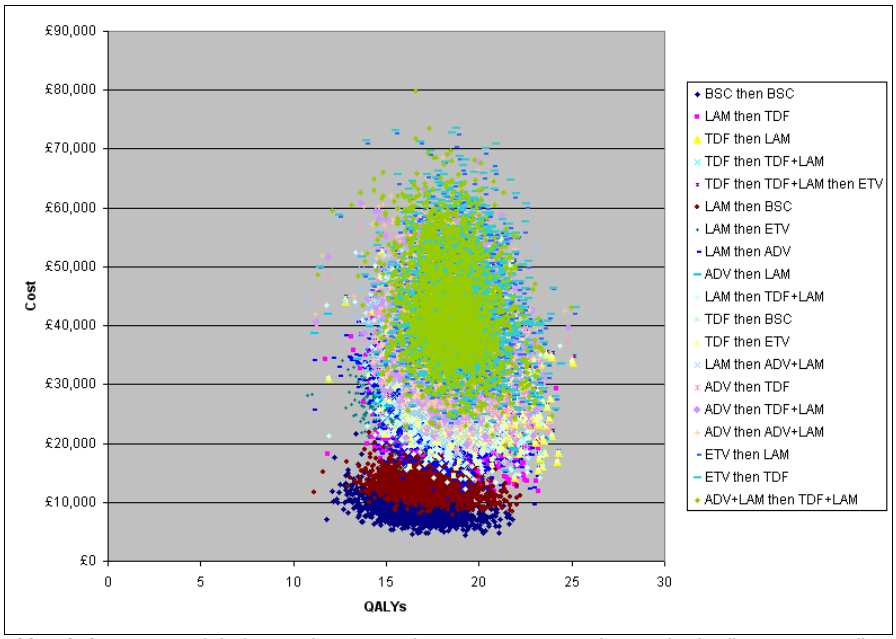
7.3.3.1. What were the main findings of the sensitivity analyses?

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.

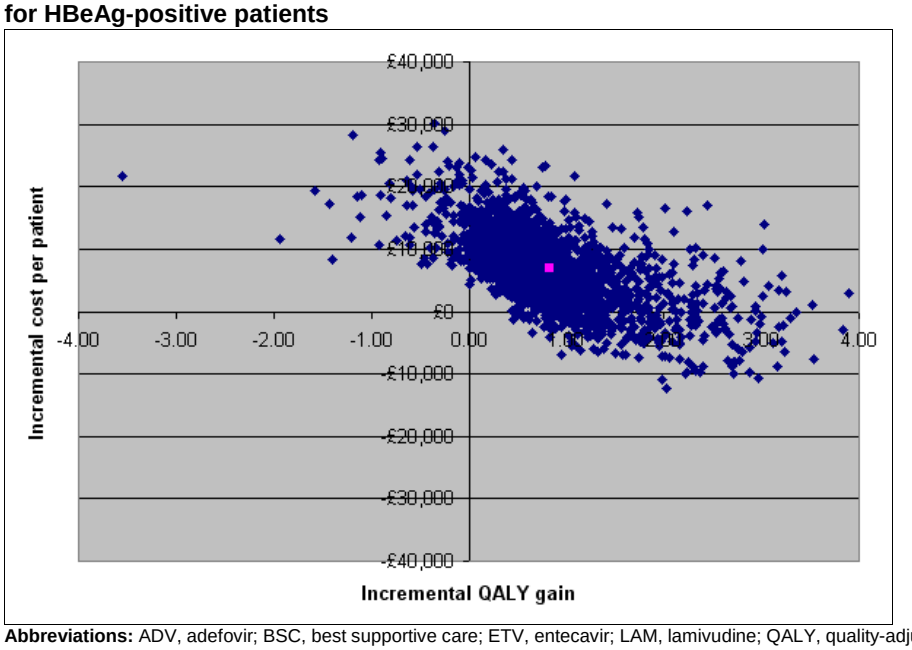
Only the main results of PSA are presented here. However, the spreadsheet model accompanying this submission enables PSA to be conducted on any plausible treatment strategy and allows generation of cost-effectiveness planes and curves for any pairwise or multiple-treatment comparisons.

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



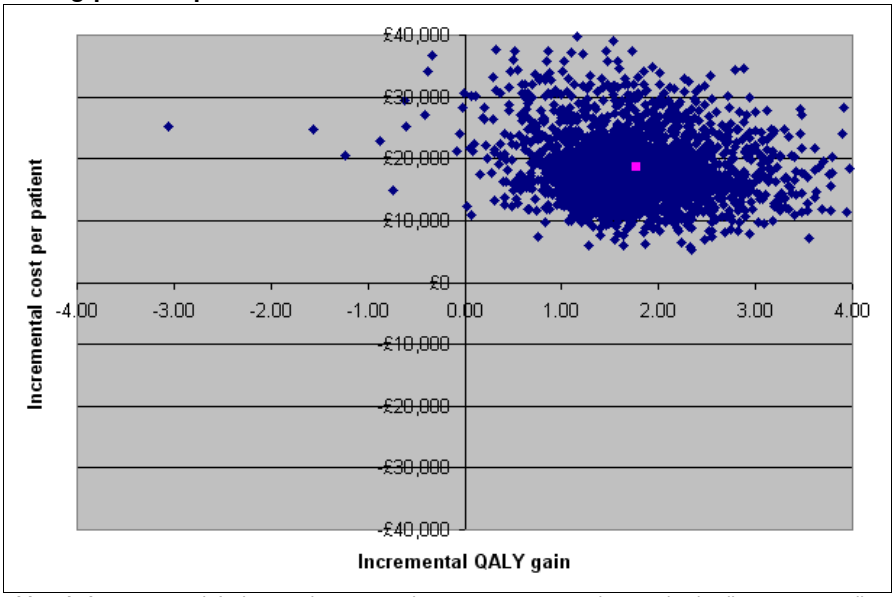
Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

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	£26,165	#	£240,042	0.00%	0.00%	3.30%	10.00%	21.95%

	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**
TDF+LAM then ETV								
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%
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%

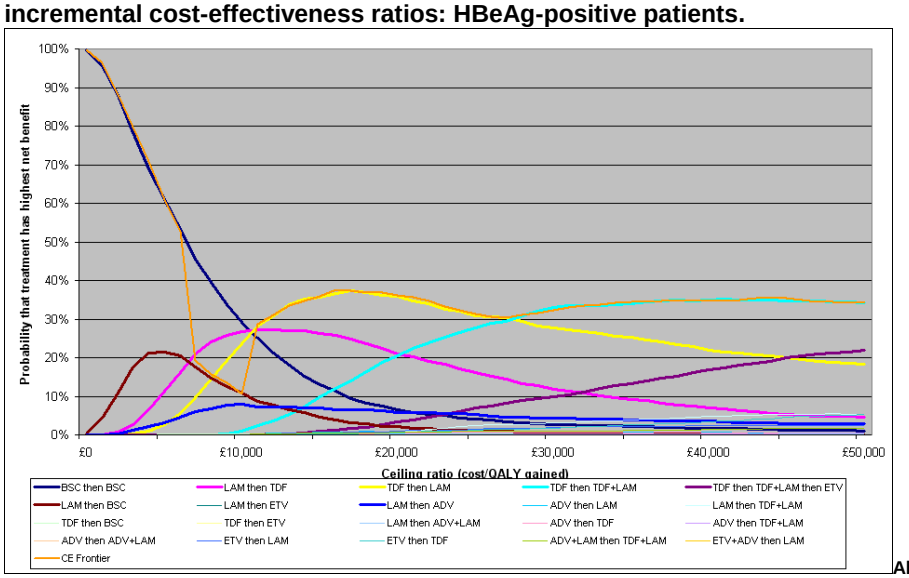
Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.
Values shown in blue typeface indicate that the treatment(s) in question has/have the highest probability of being cost-effective at this threshold.
* The "mean" 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.

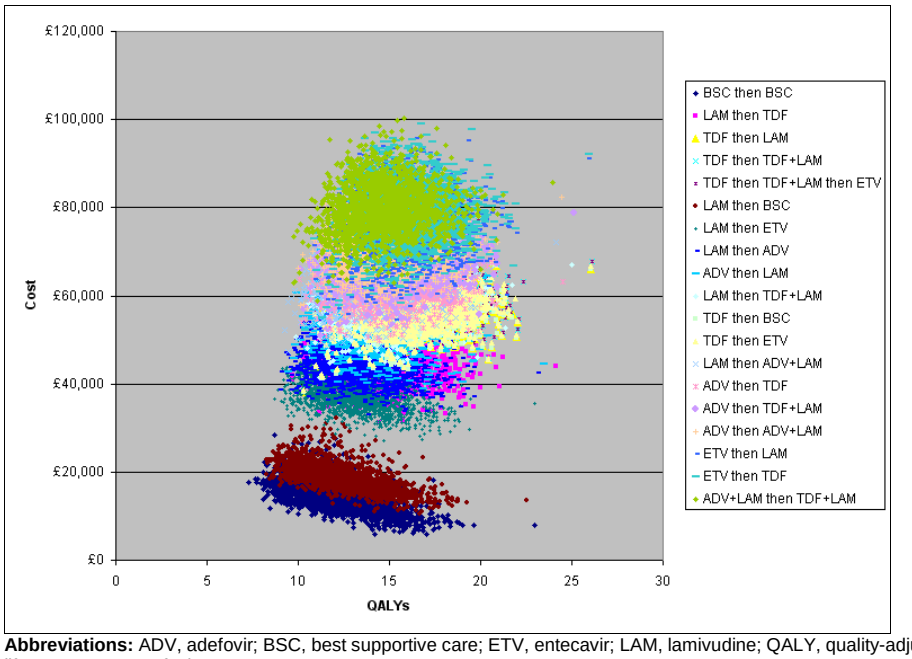
This analysis also demonstrated that the comparisons between different strategies including first-line tenofovir are extremely sensitive to model inputs: although at a £20,000/QALY ceiling ratio there is a 69% probability that lamivudine then BSC is cost-effective relative to BSC, a 68% probability that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

[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%.

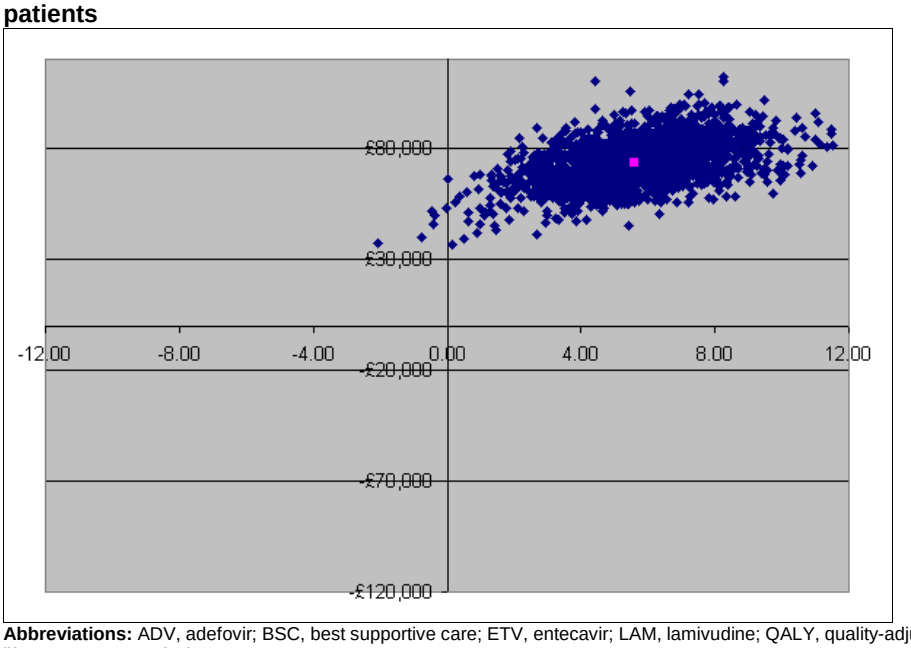
Figure 13: Scattergraph/cost-effectiveness plane plotting the total lifetime cost per patient against the total number of QALYs per patient for each of the 20 treatments considered in PSA



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

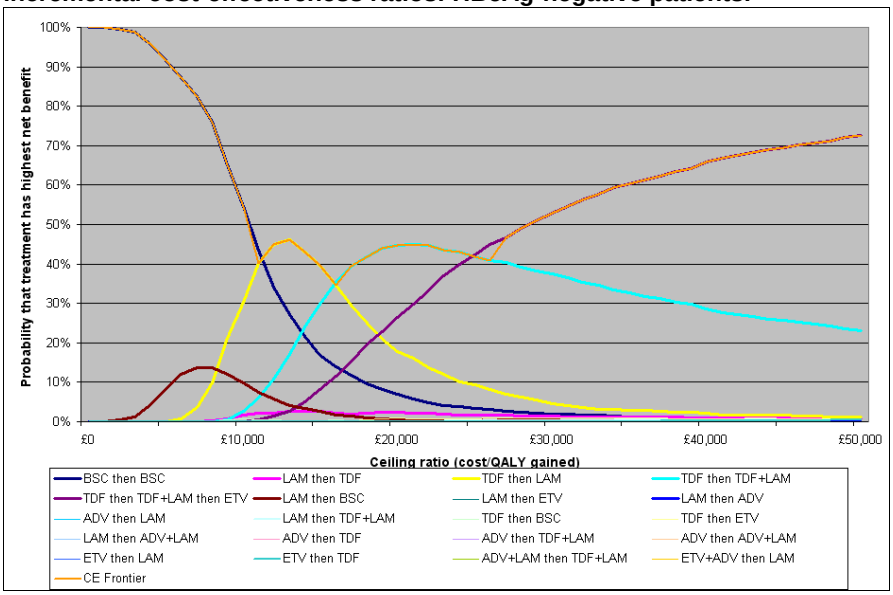
Figure 14: Cost-effectiveness plane plotting the incremental costs against the incremental benefits for tenofovir then lamivudine vs BSC for HBeAg-negative

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%

	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**
TDF then TDF+LAM	£16,083	£9,819	£47,066	0.00%	2.70%	44.70%	37.60%	23.10%
TDF then TDF+LAM then ETV	£16,108	£9,821	£47,176	0.00%	0.10%	26.55%	52.90%	72.65%
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.