NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Everolimus for preventing organ rejection in liver transplantation

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- What treatment regimens are used in clinical practice in England as maintenance immunosuppressive therapy following liver transplantation?
  - How are standard dose tacrolimus and reduced dose tacrolimus defined and how are they used in clinical practice?
  - In its model, the company compared everolimus in combination with ‘reduced’ dose tacrolimus with mycophenolate mofetil or azathioprine in combination with standard dose tacrolimus. Are these comparisons relevant to clinical practice?
  - Does standard practice include treatment with azathioprine in combination with ciclosporin, or mycophenolate mofetil in combination with reduced dose tacrolimus/reduced dose ciclosporin?

- What is the Committee's view of the robustness of the results from study H2304 and the outcomes used?
  - The results suggest that at 12 and 24 months the everolimus treatment regimen was non-inferior to the standard dose tacrolimus regimen for the primary outcome of treated biopsy proven acute rejection (tBPAR), graft loss or death, and provided superior renal function.
  - However, the primary outcome combined the efficacy of 2 outcomes which worked in different directions relative to the comparator, that is, there were fewer episodes of graft rejection in the everolimus arm but no differences in the rate of graft loss or the rate of death.
  - The ERG's clinical advisers stated that although the number of acute rejections is a relevant endpoint, these are common and easily treated and long-term survival is a more appropriate outcome for evaluating the effectiveness of immunosuppressive therapies

- Does the Committee consider that the results of the H2304 study are generalisable to the population who will receive everolimus in clinical practice in England?
  - the study was predominantly conducted in the US and included [redacted]
  - The "reduced" tacrolimus dose was equivalent to what is considered standard dose tacrolimus in the UK
  - Is the comparator arm treatment (standard dose tacrolimus) relevant to clinical practice in the NHS?
  - The mean estimated glomerular filtration rate (eGFR; a measure of renal dysfunction) was 81 mL/min/1.73 m^2 (defined as stage 1-2 chronic kidney disease (CKD); over 90 mL/min/1.73 m^2 is considered normal).
  - The proportion of people in the trial with hepatitis C virus was 31.8% in the everolimus arm and 31.3% in the standard dose tacrolimus arm. For hepatocellular carcinoma, the proportions were 17.1% and 14.4% respectively. Are the underlying reasons for transplantation in the trial representative of clinical practice?

- In the absence of direct evidence against the comparators listed in the scope, the company conducted a network meta-analysis. The ERG could not verify which data were used for the analysis of specific outcomes because of a lack of clarity in the company submission and it was unclear which studies had been included in the analysis for the tBPAR outcome. In addition the ERG noted that many of the studies used in the network meta-analysis had substantially different tacrolimus dosing levels to UK clinical practice. What is the Committee's view of the trial data incorporated into the network meta-analysis, the validity of the network meta-analysis, and the conclusions that can be drawn about the clinical effectiveness of everolimus in combination with reduced dose tacrolimus compared with the other immunosuppression therapies?

Cost effectiveness

- What are the Committee's views on the structural assumptions used by the company? The ERG had a number of concerns, including:
    - a patient simulation state-transition model may not have been required
    - the focus of the company's economic case was the renal sparing effect of everolimus in combination with reduced dose tacrolimus. Therefore, more emphasis should have been placed on the renal component of the model, and the interaction between the core hepatic model and the renal model
    - the time horizon of 80 years was unnecessarily long because after 40 years (when the average age was 94 years), 100% of patients had died
    - the clinical plausibility of the 'Mild Chronic Rejection' health state included in the model was unclear
    - overall survival was underestimated in the model
    - clinically implausible results were generated from the model, for example, some patients started the model with negative levels of eGFR.

- The ERG was concerned about the clinical inputs used by the company in the model. It found that some of the parameters differed from the ones reported in the submission and that some assumptions made with regards to resource use and drug effectiveness on renal outcomes should be further tested and validated. Is the Committee satisfied with the company's approach?

- The ERG was concerned about the lack of stability in the base case incremental cost-effectiveness ratios (ICERs) because when the ERG re-ran the company's model using the same assumptions and the same number of simulations, there was considerable variation in the results, especially for the everolimus treatment regimen compared with the mycophenolate mofetil regimen, which varied from £110,797 to £120,651 per QALY gained (nearly a 9% change). What is the Committee's view on the robustness of the company's cost-effectiveness results?

Other issues

- Is everolimus (in combination with reduced-dose tacrolimus) an innovative technology?

- Are there any equality-related issues when considering everolimus plus reduced dose tacrolimus for preventing organ rejection in allogeneic liver transplantation?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of everolimus within its licensed indication for preventing organ rejection in allogeneic liver transplantation.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	Adults undergoing allogeneic liver transplantation	Adults on maintenance immunosuppressive therapy following allogeneic liver transplantation.	Everolimus is a component of immunosuppressive therapy for the prophylaxis of graft rejection after liver transplantation. Initiation of treatment begins 4 weeks after transplantation; therefore the submission addresses maintenance therapy only. The UK indication is everolimus for the prophylaxis of organ rejection in patients receiving a hepatic transplant. In liver transplantation, everolimus should be used in combination with tacrolimus and corticosteroids.	The ERG considered that focusing on the period after transplantation was appropriate because it reflected the marketing authorisation for everolimus.
Intervention	Everolimus in combination with tacrolimus and a corticosteroid	Everolimus in combination with reduced dose tacrolimus with or without corticosteroids.	The clinical evidence informing the submission relates to everolimus in combination with reduced dose tacrolimus. In clinical practice corticosteroids are withdrawn or reduced in dose depending on patient response in order to reduce the risks of long-term adverse events associated with corticosteroid use.	The ERG considered that the specification of reduced tacrolimus seemed appropriate because it reflected the marketing authorisation. However, it commented that the reduced tacrolimus dose in the H2304 trial was the equivalent to the standard dose of tacrolimus in UK practice. The ERG considered that the exclusion of corticosteroids after 6 months of immunotherapy was appropriate because 90% of patients would be on corticosteroid-free therapies by then.

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Comparators	Standard immunosuppressive therapy with a calcineurin inhibitor (such as ciclosporin or tacrolimus) and a corticosteroid, in combination with: • azathioprine; or • mycophenolic acid.	Tacrolimus in combination with azathioprine or mycophenolate mofetil with or without corticosteroids.	Clinical practice for post-liver transplant immunosuppression in the UK is based on tacrolimus combination regimens. Mycophenolate mofetil is specified in the submission because mycophenolate sodium (an alternate presentation of mycophenolic acid) does not have a licence in liver transplantation.	The ERG agreed with the exclusion of ciclosporin because it is used as part of the treatment regimen in approximately 7% of patients and is not considered a first-line treatment. The ERG did not see a valid reason to specify the type of mycophenolate in the inclusion criteria and that the broad term mycophenolate acid could have been used which includes both mycophenolate sodium and mycophenolate mofetil. The ERG stated that even though mycophenolate sodium and mofetil cannot be interchangeably used, the active ingredient is the same and only a dose adjustment is necessary. The ERG considered that the exclusion of corticosteroids after 6 months was appropriate. The ERG commented that to truly isolate the effect of everolimus in terms of its renal sparing effect, the most appropriate comparator would be reduced dose tacrolimus.

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Outcomes	• patient survival • graft survival • graft function • graft fibrosis • time to acute rejection • time to recurrence of hepatocellular carcinoma • renal function • time to end-stage renal disease • adverse effects of treatment • health-related quality of life	The economic analysis includes the outcomes listed in the scope with the exception of two: • Graft function / fibrosis • Time to recurrence of hepatocellular carcinoma	Expert opinion advised that in clinical experience there was limited evidence to differentiate between interventions with regard to graft function and draft fibrosis. Long-term data from the pivotal everolimus trial with regard to these outcomes is presented in the body of the submission. Following the ERG's request for clarification, the company reported that time to recurrence of hepatocellular carcinoma was included in the searches as a relevant outcome but that it was not possible to include this outcome in the network meta-analysis for comparators.	The ERG agreed that it was acceptable to omit graft function and fibrosis because their definition is not standardised and they are difficult to measure. In addition, the impact of immunosuppressive therapy on graft function and fibrosis would only become apparent at around year 3 of treatment. Similarly, time to recurrence of hepatocellular carcinoma would only become apparent after 2 years of therapy. Therefore the trial would not necessarily capture the impact of everolimus in combination with reduced dose tacrolimus on these outcomes.

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Economic analysis	The cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Cost-effectiveness expressed as incremental cost per quality-adjusted life year, with a lifetime horizon, considering costs from an NHS and Personal Social Services perspective.	In line with scope.	The time horizon considered in the economic model was lifetime (80 years). The ERG considered that, given that the average starting age of patients in the economic model was 54 years (with a standard deviation of 10 years), the time frame seemed high. At around year 40 of the analysis 100% of patients would have died.

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Subgroups to be considered	People with hepatitis C infection. People with renal dysfunction.	Renal dysfunction is modelled but is not included as a subgroup. Hepatitis C is not included as a subgroup in the model.	Patients with Hepatitis C were not included in the model after clinical advisers stated that no differences in recurrence rates or treatment between treatment arms would be expected following liver transplantation. The model includes a renal sub-model, which allows patients to transition through the stages of chronic kidney disease. However, it does not include specific cost-effectiveness results for people with renal dysfunction.	No comments

2 The technology and the treatment pathway

2.1 After a liver transplant, life-long treatment with immunosuppressant drugs is needed, with the aim to reduce the risk of organ rejection while minimising the adverse effects of treatment such as impaired kidney function, higher risk of cardiovascular disease, infections, osteoporosis and cancer. If rejection does occur; then it is managed with the goal of the patient returning to a 'Stable post-transplant' state'. Adjustments to immunosuppressant dosing may need to be made to treatment in response to more long-term post-transplant complications such as renal dysfunction.

2.2 No NICE clinical guidelines or technology appraisals have been published on the management of patients following a liver transplant. The company highlighted that variations may exist between centres with regard to choice of immunosuppressive therapy and the long-term management of treatment in relation to dose adjustment since there are no national protocols on the management of patients post liver transplant. However, the company recognised that the British Transplantation Society (BTS) had published guidelines for the management of liver transplantation for patients with non-alcoholic steato-hepatitis (NASH) before and after liver transplantation which includes recommendations on immunosuppression post-transplant.

2.3 The European Medicine's Agency guideline on clinical investigation of immunosuppressants for solid organ transplantation from 2009 stated that immunosuppressive regimens often begin with a short induction phase, usually with ciclosporin, corticosteroids or basiliximab, followed by post-transplant and maintenance therapy. Triple therapy with calcineurin inhibitors such as ciclosporin or tacrolimus, in combination with a corticosteroid (prednisolone) and an antiproliferative agent such as azathioprine, mycophenolate mofetil or sirolimus are normally given after the induction phase. After a period of successful prevention of transplant rejection, the dosages or number of immunosuppressants given may be

reduced (that is, dual therapy may be considered) depending on the patient's needs.

2.4 Everolimus (Certican, Novartis Pharmaceuticals UK) is an immunosuppressant analogue of sirolimus that inhibits the mammalian target of rapamycin (mTOR) protein and targets the primary causes of progressive allograft dysfunction (also known as chronic rejection) following organ transplantation. It has a marketing authorisation in the UK for the prophylaxis of organ rejection in patients receiving a hepatic transplant. In liver transplantation, everolimus is used in combination with tacrolimus and corticosteroids and it is administered orally. The summary of product characteristics (appendix A) states that for people who have had a liver transplant, exposure to tacrolimus should be reduced to minimise calcineurin-related renal toxicity. The tacrolimus dose should be reduced starting approximately 3 weeks after initiating administration together with everolimus, based on targeted tacrolimus blood trough levels of 3-5 ng/ml. In a controlled clinical trial, complete withdrawal of tacrolimus has been associated with an increased risk of acute rejections.

The company stated that everolimus will fit into the existing post-transplant clinical pathway by offering an alternative choice of immunosuppressive therapy.

Table 2 Technology

	Intervention	Comparators
Treatment name	Everolimus in combination with reduced dose tacrolimus, with or without corticosteroids	Tacrolimus in combination with azathioprine or mycophenolate mofetil, with or without corticosteroids
Marketing authorisation	Everolimus has a marketing authorisation for the prophylaxis of organ rejection in patients receiving a hepatic transplant. In liver transplantation, everolimus should be used in combination with tacrolimus and corticosteroids. The tacrolimus dose should be reduced starting approximately 3 weeks after initiating administration together with everolimus, based on targeted tacrolimus blood trough levels of 3-5 ng/ml	Tacrolimus has a marketing authorisation for the prophylaxis of transplant rejection in liver, kidney or heart allograft recipients and the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products. Azathioprine has a marketing authorisation as an immunosuppressant antimetabolite to enhance the survival of organ transplants (such as hepatic transplants); and to reduce the corticosteroid requirements of renal transplant recipients. Mycophenolate mofetil has a marketing authorisation in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplant
Acquisition cost (according to the British National Formulary January 2015, apart from everolimus which was provided by the	Everolimus: 0.25mg x 60 £148.50 0.5mg x 60 £297.00 0.75mgx 60 £445.50 Tacrolimus cost in the company's economic model was based on Prograf (Astellas), 1 mg x100 £160.54 (other	The cost of tacrolimus in the company's economic model was based on Prograf (Astellas). 1 mg x100 £160.54 (other preparations available). Azathioprine 50mg x 56 tablets £3.42 Intravenous mycophenolate mofetil (CellCept) 500mg x 1 vial £9.12. Oral mycophenolate mofetil 500mg x 50 £11.82

company. All costs excluding VAT)	preparations available). Prednisolone 5mg x 28 £1.31	Prednisolone 5mg x 28 £1.31
Dosing frequency	Everolimus: the summary of product characteristics states that everolimus is initiated at a daily dose of 2.0 mg (1.0 mg twice daily) approximately 4 weeks after transplantation with the dose targeted to remain at a trough level of 3 to 8 ng/mL. The tacrolimus dose of100-200 micrograms/kg daily should begin 12 hours after transplantation and reduced after 3 weeks when taken with everolimus with dose targeted at a trough level of 3-5 ng/mL. The company submission assumed that 5mg corticosteroids were taken daily for first 6 months.	Tacrolimus: the summary of product characteristics states that therapy should start 12 hours after transplantation, with 100-200 micrograms/kg daily. Doses are usually reduced in the post-transplant period. In the H2304 study for the comparator arms, tacrolimus trough levels were targeted to be maintained at 8 – 12 ng/mL until Month 4. At Month 4, tacrolimus was tapered to a target trough level of 6 – 10 ng/mL for the remainder of the study. Azathioprine: the summary of product characteristics recommends that a dosage of up to 5 mg/kg bodyweight/day may be given on the first day of therapy, either orally or intravenously. Maintenance dosage should range from 1-4 mg/kg/bodyweight/day and must be adjusted according to clinical requirements and haematological tolerance. Mycophenolate mofetil: IV 1g twice daily within 24 hours of transplantation for 4 days followed by (oral) 1.5g twice daily as tolerated. The company submission assumed that 5mg corticosteroids were taken daily for first 6 months
Monitoring costs	No ongoing monitoring costs were included in the company's economic model as it was assumed that that these were included in the consultations costs	

See summary of product characteristics for details on adverse reactions and contraindications.

3 Comments from consultees

3.1 The patient expert group stated that the reason for transplant can vary according to disease type, including cancer, alcohol, viral hepatitis, fatty liver (obesity), auto-immune diseases and acute liver failure. They stated that for all people who receive a liver transplant there is a lifelong commitment to taking a daily regimen of pills, while dealing with the fact that they are grateful to be alive, and have received a liver transplant. People who have had a liver transplant tend not to have a preference regarding the immunosuppressants they take, and rely on clinicians to decide the most appropriate medicine for them.

3.2 The patient expert group highlighted that treatment outcomes that are most important to people who have had a transplant are that they can regain the standard of living they had before their liver transplant, and that the chance of organ rejection is minimised as far as possible.

3.3 The patient expert group commented that for certain groups of transplant recipients (people with hepatitis C and hepatocellular carcinoma), everolimus will be beneficial. The patient expert group highlighted the importance of clinicians having a wide range of options when deciding the most appropriate treatment after a transplant.

3.4 The clinical expert stated that across the UK there is broad consensus that most patients will receive a combination of tacrolimus, an antiproliferative agent such as azathioprine or mycophenolate mofetil, and corticosteroids. The clinical expert highlighted that patients at higher risk of renal dysfunction may receive induction therapy which includes monoclonal antibodies or intravenous mycophenolate mofetil to allow for delayed introduction of tacrolimus. However, there is variation across liver units in use of induction regimens, choice of anti-metabolites and duration of treatment with anti-metabolites/steroids. Another strategy to reduce renal dysfunction has been a move towards minimising dose of tacrolimus (and other calcineurin inhibitors such as ciclosporin), although there is

variation in how this is achieved. For example, sirolimus is used by some units to minimise use of calcineurin inhibitors.

3.5 The clinical expert highlighted that the potential advantage of everolimus could be to preserve renal function. They also stated that there are recognised groups of patients that have a different prognosis following a liver transplant, and in particular in relation to levels of renal dysfunction. Therefore, some groups may benefit differently from everolimus. Some examples are:

- Patients receiving Donation after Cardiac Death (DCD) liver transplants
- Patients receiving a second (or subsequent) liver graft
- Patients receiving a transplant for acute liver failure
- Patients undergoing combined transplantation with an organ additional to liver
- Patients with renal dysfunction
- Patients with chronic hepatitis C infection (although this may change in the light of new anti-viral therapies becoming available)

3.6 The clinical expert commented that the use of everolimus in the published clinical studies reflects how it would be used in clinical practice in the UK.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company's systematic review identified 1 randomised controlled trial of everolimus for preventing organ rejection following liver transplantation that it considered relevant to the decision problem. Study H2304 included 719 people and was predominantly conducted in the US, with a limited number of UK patients [redacted]. The company did not identify any non-RCT evidence that was relevant to the decision problem.

4.2 Study H2304 was a 24-month multicentre, open-label randomised controlled study that evaluated the efficacy and safety of everolimus in combination with reduced dose tacrolimus compared with standard dose

tacrolimus. It included people aged 18 to 70 years who had received a primary liver transplantation and had been initiated on an immunosuppressive regimen containing tacrolimus and corticosteroids 3–7 days post-transplantation (see section 6.3.3 of the company submission for the full inclusion/exclusion criteria). Patients were randomised at 30 days (±5 days) post-transplantation, to one of the following treatment arms:

- Arm 1: everolimus initiation with tacrolimus elimination. This arm of the trial was stopped early due to a higher rate of acute rejection and treatment discontinuations and was excluded from further discussion in the company submission.
- Arm 2: everolimus initiation with reduced dose tacrolimus: everolimus was initiated at a daily dose of 2.0 mg 30 days post transplant and the dose was targeted to be maintained at a trough level of 3-8 ng/mL. After everolimus whole blood trough levels were confirmed to be in the target range, tacrolimus was tapered to achieve a target trough level of 3-5 ng/mL by 3 weeks after randomisation and continuing for the remainder of the study.
- Arm 3: standard dose tacrolimus: tacrolimus trough levels were targeted to be maintained at 8-12 ng/mL until month 4 and were then tapered to a target trough level of 6-10 ng/mL for the remainder of the study.

4.3 Prednisolone (30 days post-transplant) was given at a minimum dose of 5 mg per day at the time of transplant and for at least 6 months. Prior to randomisation, 70% of people in both treatment groups were receiving mycophenolate mofetil but were discontinued at randomisation according to protocol. However, people receiving azathioprine and sirolimus were excluded from the study. Baseline characteristics appeared similar between the treatment arms, see table 8 on page 56 of the company submission and response to A19 of the clarification question for a full breakdown of the baseline characteristics. The proportion of people in the

trial with hepatitis C virus was 31.8% in the everolimus arm and 31.3% in the standard dose tacrolimus arm. For hepatocellular carcinoma, the proportions were 17.1% and 14.4% respectively.

4.4 The inclusion criterion for baseline eGFR was ≥30 mL/min/1.73 m^2. Randomised patients had a mean eGFR of 81 mL/min/1.73 m^2, which, according to the company's clinical expert, is higher than the eGFR levels typically observed in patients in clinical practice in the UK (usually in the range of 50–65 mL/min/1.73m^2 at the time of liver transplant).

4.5 The primary outcome was a composite of treated biopsy proven acute rejection (tBPAR), graft loss or death at 12 months post transplantation (excluding events before randomisation). This was presented as the Kaplan Meier incidence rate, with the difference being determined at the 97.5% confidence interval. Secondary outcomes included graft loss, death, graft rejection endpoints and change in renal function measured by estimated glomerular filtration rate (eGFR). The full list of the secondary outcomes is provided in Appendix 16 of the company's submission. No patient-related outcomes such as health-related quality of life were measured in the trial.

4.6 Statistical analysis performed in the H2304 trial was designed to show the non-inferiority of everolimus in combination with reduced dose tacrolimus compared with standard dose tacrolimus in terms of the composite of tBPAR, graft loss, or death at 12 months. A pre-determined non-inferiority margin of 12% was used in the analysis for the primary outcome based on a $p<0.001$ value. Non-inferiority was demonstrated if the upper limit of the 97.5% confidence interval for the difference between the two groups was below 12%. For the outcome of graft loss or death, a non-inferiority margin of 10% was used. The statistical analyses for Study H2304 are summarised in section 6.3.6 of the company submission.

ERG comments

4.7 The ERG considered that all studies relevant to the decision problem were included in the company's submission. It commented that the searches were limited to studies of ciclosporin or tacrolimus in combination with everolimus, azathioprine or mycophenolate mofetil. Therefore, any studies that evaluated the efficacy of everolimus as a stand-alone intervention would be missed by this search but it noted that this was outside the marketing authorisation. Overall, the ERG was satisfied with the company's attempts to locate published and unpublished evidence from randomised-controlled trials.

4.8 The ERG noted that the clinical effectiveness of everolimus relied upon evidence drawn from the H2304 trial, which it considered was of good quality. However, it considered that the efficacy endpoints used in the trial might not be the most appropriate ones. Clinical opinion sought by the ERG explained that, although the number of acute rejections is a relevant endpoint, these are common and easily treated and long-term survival is a more appropriate outcome for evaluating the effectiveness of immunosuppressive therapies. The ERG also noted the lack of a health questionnaire to directly capture patients' health-related quality of life.

4.9 The ERG noted the company's acknowledgement that target ranges for reduced dose tacrolimus in study H2304 (3 to 5 ng/mL) were higher than in standard UK clinical practice (where trough levels <5 ng/mL are considered as low-dose tacrolimus). The company explained that this was because the trial was conducted predominantly in the US and because of changes in clinical practice since 2007. The ERG highlighted that in general the average trough levels of tacrolimus were higher than the ones initially planned for all arms of the trial and that the reduced dose tacrolimus arm showed trough levels above 5ng/mL throughout the 12 months. Clinical advisers to the ERG explained that a standard dose tacrolimus regimen in the UK is 6-8 ng/mL until month 1, just above 6 ng/mL until month 4 and between 5 and 6 ng/mL until the end of the first

year. The ERG therefore considered that the reduced tacrolimus dose in the H2304 trial was equivalent to the standard dose of tacrolimus in UK practice. It also noted that in the discontinued tacrolimus elimination arm of the trial (see section 4.2), the tacrolimus trough levels were closer to what would be considered a reduced level of tacrolimus in the UK. It therefore questioned whether the tacrolimus elimination arm of the trial, and its outcomes, would be more appropriate to capture the advantage of everolimus and its renal sparing effect within the UK.

4.10 The ERG considered that the company's overall approach to the statistical analysis of H2304 was generally sound. The ERG highlighted that in non-inferiority trials, the choice of the non-inferiority margin is crucial. However, the ERG commented that it could not find a justification for the non-inferiority margin used since the company did not explain their decision in their submission.

Clinical trial results

4.11 The company submission included results for the intention-to-treat (ITT) population from study H2304 for 12 and 24 months follow up. For the primary composite efficacy endpoint of tBPAR, graft loss or death, everolimus in combination with reduced dose tacrolimus was statistically non-inferior to standard dose tacrolimus because the upper limit of the confidence interval was below the 12% non-inferiority margin for this outcome and the p value was reported to be <0.001. At 12 months the Kaplan–Meier survival probability was 93.3% compared with 90.3%, 97.5% confidence interval (CI) for the difference -8.7 to 2.6; p-value for non-inferiority <0.001). At 24 months the Kaplan–Meier survival probability was 89.7% compared with 87.5%, 97.5% CI for the difference -8.8 to 4.4; p-value for non-inferiority [redacted].

4.12 For the outcome of graft loss or death, everolimus in combination with reduced dose tacrolimus was statistically non-inferior to standard dose tacrolimus because the upper limit of the confidence interval was below the 10% non-inferiority margin for this outcome. At 12 months, the

Kaplan–Meier survival probability was [redacted]. At 24 months, the Kaplan–Meier probabilities were 92.7% and 93.8% respectively, 97.5% CI for the difference -4.2 to 6.4; p-value for non-inferiority [redacted]

4.13 There were no statistically significant differences between treatment groups in the rate of graft loss or in the rate of death at 12 or 24 months (p-values > 0.05). However, there were statistically significantly fewer episodes of rejection at 12 months in the group randomised to everolimus in combination with reduced dose tacrolimus compared with the group randomised to standard dose tacrolimus. At 12 months, the Kaplan–Meier tBPAR free probability was 96.3% in the everolimus group compared with 89.3% in the standard dose tacrolimus group, 95% CI for the difference –11.6 to -2.5; p-value <0.003. At 24 months, the Kaplan–Meier probabilities were 93.9% and 86.7% respectively, 95% CI for the difference -13.5 to -0.9; p-value = 0.01.

4.14 The efficacy results for 12 and 24 months post-transplantation are summarised in table 3.

Table 3 Clinical trial results for Study H2034 at 12 months (ITT population)
(adapted from table 9 of the company's submission)

	EVR+ Reduced TAC (N=245)	**TAC Control (N=243)**	**Difference (SE) (95% CI)**	**p Value (No difference test)**	**P Value (non-inferiority test)**
Time to death					
KM survival probabilities (%)	96.3	97.5	1.2 (NR) (-7.8 to 10.1)	p=0.60	-
Number of deaths*	9	6			
Crude death (%)	3.7	2.5			
Time to graft loss or death					
KM graft survival probabilities (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]*
Number of patients with graft loss	[redacted]	[redacted]			

Time to tBPAR or death					
KM tBPAR free probabilities (%)	97.1	93.0	-4.1 (NR) (-8.0 to -0.3)	p=0.035	-
Number of patients with tBPAR reported	7	17			
Time to acute rejection					
KM tBPAR free probabilities (%)	96.3	89.3	-7.0 (NR) (-11.6 to -2.5)	p=0.003	-
Number of patients with acute rejection reported	9	26			
Time to death or loss graft loss or tBPAR					
KM composite efficacy survival probabilities (%)	93.3	90.3	-3.0 (NR) (-8.7 to 2.6)	p [redacted]	<0.001**
Number of composite events	16	23			

* non-inferiority margin of 10% was used
**non-inferiority margin of 12% was used
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; EVR, everolimus; KM, Kaplan-Meier; NR, not reported; SE, standard error; TAC, tacrolimus; tBPAR, treated biopsy proven acute rejection;

Table 4 Clinical trial results for Study H2034 at 24 months (ITT population)

(adapted from table 10 of the company's submission

	EVR+ Reduced TAC	**TAC Control**	**Difference (SE) (95% CI)**	**p value (No difference)**	**p value (non-inferiority)**
Time to death					
KM survival probabilities (%)	94.8	95.6	0.8 (NR) (-3.7 to 5.2)	p=0.70	-
Number of deaths*	12	10			
Time to graft loss or death					
KM graft survival probabilities (%)	92.7	93.8	1.1 (NR) (-4.2 to 6.4)	p=0.64	[redacted]*
Number of patients with graft loss*	17	14			
Time to tBPAR or death					
KM tBPAR free probabilities (%)	95.2	92.3	-2.9 (NR) (-7.9 to 2.2)	p=0.20	-
Number of patients with tBPAR reported	11	18			

Time to acute rejection (incidence of BPAR)					
KM tBPAR free probabilities (%)	93.9	86.7	-7.2 (NR) (-13.5 to -0.9)	p=0.01	-
Number of patients with acute rejection reported*	14	30			
Time to death or loss graft loss or tBPAR					
KM composite efficacy survival probabilities (%)	89.7	87.5	-2.2 (NR) (-8.8 to 4.4)	p=0.45	[redacted]**
Number of composite events*	24	29			

* non-inferiority margin of 10% was used
**non-inferiority margin of 12% was used
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; EVR, everolimus; KM, Kaplan-Meier; NR, not reported; SE, standard error; TAC, tacrolimus; tBPAR, treated biopsy proven acute rejection;

4.15 Everolimus in combination with reduced dose tacrolimus provided superior renal function compared with a standard dose tacrolimus regimen at 12 and 24 months after liver transplantation. The difference in mean eGFR was 8.50 mL/min/1.73m2 (p<0.001, 97.5% CI 3.74 to 13.27) at month 12 and 6.66 mL/min/1.73m2 (p<0.001, 97.5% CI 1.90 to 11.42) at month 24 (see table 5).

Table 5 - Change in renal function measured by eGFR (adapted from tables 9 and 10 of the company's submission)

	EVR+ Reduced TAC (N=245)	**TAC Control (N=243)**	**Difference (SE) (95% CI)**	**p Value**
Change in eGFR from randomisation at 12 months post liver transplantation				
Change in renal function from baseline*	-2.23 (se=1.54)	-10.73 (se=1.54)	8.5 (2.12) (3.74 to 13.27)	p ≤0.001 (demonstrating statistical non-inferiority and superiority)
Change in eGFR (MDRD4) from randomisation at 24 months post liver transplantation				
Change in renal function from baseline*	-7.9 (se=1.5)	-14.6 (se=1.5)	6.7 (2.1) (1.9 to11.4)	p ≤0.0001

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; EVR, everolimus; MDRD4, four-variable modification of diet in renal disease; SE, standard error; TAC, tacrolimus

4.16 The company presented results for a number of pre-defined subgroup analyses including subgroups based on age, gender, race, eGFR, hepatitis C status, and cause of end-stage liver disease. Incidence rates of primary composite outcome (time to treated BPAR, graft loss or death) are presented in tables 11 and 12 of the company's submission. The company reported that the overall pattern of the event rates within subgroups was similar to that observed in the overall population. Within these subgroup analyses in H2304, the company reported that there were no statistically significant differences in the incidence of hepatocellular carcinoma or hepatitis C virus recurrence or hepatitis C virus-related fibrosis progression between everolimus plus reduced dose tacrolimus and the control tacrolimus arm.

ERG comments

4.17 The ERG found inconsistencies in the company submission in the reporting of the results from study H2304 and therefore used the clinical study reports to critique the main efficacy and safety results. The ERG also presented limited results for 36 months follow up because these were not included in the company submission; these are presented in table 15 of the ERG report.

4.18 The ERG noted that the composite primary outcome of the trial (tBPAR, graft loss and death) combined the effectiveness of two outcomes which worked in different directions relative to the comparator. The ERG commented that whilst the results for the outcome of graft loss or death favoured the standard dose tacrolimus arm of the trial, the addition of tBPAR to the composite endpoint favoured everolimus in combination with reduced dose tacrolimus. The ERG considered that this cast doubt on the appropriateness of the composite endpoint.

4.19 The ERG noted that the statistical analysis undertaken on the secondary outcomes produced qualitatively different results from those for the primary outcome (summarised in table 11 of the ERG report). The ERG highlighted that there were no statistically significant differences between

the treatment groups in the rates of graft loss or in the rates of death at 12 or 24 months. However, there were statistically significantly fewer episodes of graft rejection in the everolimus group compared with the standard dose tacrolimus group. The ERG considered therefore that the effectiveness of everolimus was largely dependent on the choice of clinical outcomes and whether these included acute rejection episodes or graft losses.

Network meta-analyses

4.20 In the absence of direct trial evidence, the company undertook a systematic review and network meta-analysis. This estimated the relative effectiveness of everolimus in combination with reduced dose tacrolimus for preventing allogenic liver transplantation rejection in the maintenance phase compared with:

- mycophenolate mofetil (in combination with standard dose tacrolimus, reduced dose tacrolimus or standard dose ciclosporin);
- azathioprine (in combination with standard dose tacrolimus or standard dose ciclosporin);
- standard dose tacrolimus.

4.21 The company identified 22 randomised-controlled trials that assessed the efficacy of these treatments, with or without corticosteroids (see table 19 of the company submission for details of the studies). It reported that there was heterogeneity and variation between studies that provided challenges to building a feasible network, such as a lack of reporting of characteristics that were potential treatment effect modifiers, variation in the definition of the tacrolimus and ciclosporin arms with respect to dosage, variations in definitions of outcomes and variation in the duration or use of corticosteroid therapy in combination with the interventions of interest. However, the company considered that the evidence was sufficient to draw feasible networks for 13 of the 16 clinical endpoints extracted from the studies (described in table 17 of the company

submission). These included overall survival, graft survival, tBPAR, and renal function.

4.22 The company also reported some discrepancies between study H2304 and the other trials, for example more patients in H2304 had diabetes and hypertension at baseline, and the standard dose tacrolimus arm presented better overall survival, graft survival and free from tBPAR probabilities than the standard dose tacrolimus arms of other studies. The company reported that, as study H2304 was the only study of everolimus in combination with reduced dose tacrolimus, it was not possible to conduct subgroup analyses excluding this study and hence study H2304 was assumed to be comparable with the rest of the evidence.

4.23 The results of the network meta-analysis were presented as a consistency model, where direct and indirect evidence were assumed consistent for any 'closed loops' in the evidence network. An inconsistency model was also presented where data were available (that is, using direct evidence only). The company reported that all models were based on the NICE Decision Support Unit guidance 2011 and that the parameters of the different models were estimated within a Bayesian framework using a Markov Chain Monte Carlo method as implemented in the WinBUGS/OpenBUGS software package. To assess for heterogeneity in the treatment effects for a particular pair-wise comparison caused by the treatment effect modifiers, both fixed effects and random effects models were assessed.

4.24 The results for the 13 outcomes extracted from the studies were presented in tables 23 to 39 of the company's submission (as odds ratios alongside credible intervals; however only the probability of being tBPAR free and renal function were used in the economic model). In addition, the absolute results were presented by the company in their response to clarification (see tables R5 to R20 of the company's response to clarification) and are summarised below for overall survival, graft survival, tBPAR and renal function using fixed effects models.

4.25 For overall survival at 12 and 24 months, the company reported that everolimus in combination with reduced dose tacrolimus was expected to be comparable to all other treatments. It was ranked 5th and 4th amongst the interventions at 12 and 24 months respectively. At 24 months, overall survival was 85.3%, 95% credible interval 72.5 to 92.9%), compared with:

- mycophenolate mofetil in combination with ciclosporin (88.9%, 95% credible interval 43.6 to 98.8)
- mycophenolate mofetil in combination with standard dose tacrolimus (88.4%, 95% credible interval 83.8 to 92.0)
- standard dose tacrolimus (87.4%, 95% credible interval 84.1 to 90.2)
- azathioprine in combination with standard tacrolimus (85.8%, 95% credible interval 76.7 to 91.8).

4.26 For graft survival at 12 and 24 months, the company reported that everolimus in combination with reduced dose tacrolimus was expected to be comparable to all treatments. It was ranked 5th and 4th amongst the interventions at 12 and 24 months respectively. At 24 months, graft survival was 79.7%, 95% credible interval 67.3 to 88.4%), compared with:

- mycophenolate mofetil in combination with ciclosporin (86.0%, 95% credible interval 49.4 to 97.5)
- mycophenolate mofetil in combination with standard dose tacrolimus (85.3%, 95% credible interval 80.0 to 89.6)
- standard dose tacrolimus (82.6%, 95% credible interval 79.1 to 85.8)
- azathioprine in combination with standard tacrolimus (80.8%, 95% credible interval 70.6 to 88.2).

4.27 For the outcome of being tBPAR free at 3, 6 and 12 months, everolimus in combination with reduced dose tacrolimus was ranked as the best therapeutic option amongst all therapies. At 12 months, the absolute estimate was 89.5%, 95% credible interval 82.3 to 94.4%), compared with:

- mycophenolate mofetil in combination with standard dose tacrolimus (83.4%, 95% credible interval 75.8 to 88.9)
- mycophenolate mofetil in combination with reduced dose tacrolimus (80.6%, 95% credible interval 74.3 to 85.9)
- standard dose tacrolimus (76.8%, 95% credible interval 72.0 to 81.2)
- azathioprine in combination with standard tacrolimus (75.6%, 95% credible interval 65.3 to 83.7)
- azathioprine in combination with ciclosporin (72.3%, 95% credible interval 55.4 to 84.6).

4.28 For renal function at 12 months (reported in the studies as eGFR or estimated creatinine clearance [eCCR]), azathioprine in combination with ciclosporin led to the lowest decline, followed by everolimus in combination with reduced dose tacrolimus. At 12 months, the absolute estimate for everolimus in combination with reduced dose tacrolimus was -23.1 (credible interval -27.4 to -18.7), compared with:

- azathioprine in combination with ciclosporin (-14.5, credible interval -24.2 to -4.9).
- mycophenolate mofetil in combination with reduced dose tacrolimus (-28.2, credible interval -32.3 to -24.1)
- standard dose tacrolimus (-31.8, credible interval -32.3 to -30.9).

4.29 The company undertook scenario analyses, which involved removing specific trials from the network to assess the impact on the results. However, it did not present any results in its submission.

ERG comments

4.30 The ERG found that many of the studies used in the network meta-analysis had substantially different tacrolimus dosing levels to UK clinical practice. Whilst some studies maintained tacrolimus trough levels above 5ng/ml in their reduced tacrolimus dose arms, other studies maintained trough levels below 5ng/ml in their standard dose tacrolimus arms.

Therefore, no consistency was seen across studies with respect to drug levels.

4.31 The ERG questioned the validity of the network meta-analysis results for the renal outcomes because it considered that the allocation of the different studies' treatment arms to the reduced and standard tacrolimus categories was inconsistent and misleading. As the standard dose tacrolimus connector across the network meta-analysis studies was so heterogeneous, the ERG considered that the results of the network meta-analysis were not robust.

4.32 The ERG found a significant limitation in the network meta-analysis as the data included in the WinBUGS codes did not relate to the submission data and appeared to have been taken from either a different submission or a theoretical exercise. The ERG could not verify which data were used for the analysis of specific outcomes because of a lack of clarity and transparency in the company submission. The ERG stated that it was unclear which studies had been included in the analysis for the tBPAR outcome.

4.33 The ERG noted that the data ultimately used in the economic model did not consist of odds ratios but rather probability of events and it sought clarification from the company about how it derived these. The ERG reported that it was unable to verify the absolute estimates presented by the company in response to clarification because the company did not provide the WinBUGS coding to enable this.

4.34 The ERG commented that the company's scenario analyses, which consisted of removing specific trials from the network to assess the impact on the results, lacked transparency and were not informative because no results were presented.

Adverse effects of treatment

4.35 The company did not identify any studies that reported adverse events for everolimus in combination with reduced dose tacrolimus other than study

H2304. In study H2304, lipid changes occurred more frequently in the everolimus arm than in the standard dose tacrolimus arm (at 12 months, [redacted] at 24 months, 26.9% compared with 11.6%, RR 15.4, 95% CI 8.5 to 22.2). At 24 weeks, the incidence of new onset diabetes mellitus was higher in the everolimus group (20.8% compared with 16.5%, RR 4.3, 95% CI 2.6 to 11.2), as was the occurrence of biliary leaks ([redacted]) The company did not report any statistically significant differences in the occurrence of diarrhoea, headache, hypertension, wound healing/biliary leaks, new onset diabetes mellitus, infections or renal failure at 12 months. There were fewer cases of renal failure in the everolimus arm of the trial (15 compared with 21 in the standard dose tacrolimus arm at 12 months) but no tests of significance were reported. The key adverse events from study H2304 are presented in table 6.

Table 6 Key adverse events from the H2304 Study

System organ / class / adverse events	12 months			24 months		
	EVR+ rTAC (N = 245) n (%)	TAC control (N = 241) n (%)	Relative risk, % (95% CI)	EVR+ rTAC (N = 245)	TAC control (N = 241)	Relative risk, % (95% CI)
Diarrhoea	47 (19.2)	50 (20.7)	0.92 (0.65-1.32)	[redacted]	[redacted]	[redacted]
Headache	47 (19.2)	46 (19.1)	1.01% (0.70-1.45)	[redacted]	[redacted]	[redacted]
Hypertension	42 (17.1)	38 (15.8)	NR	[redacted]	[redacted]	[redacted]
Wound healing/ biliary leaks	27 (11)	19 (7.9)	1.4 (0.80-2.45)	27 (11)	20 (8.3)	2.8 (2.5-8.0)
New onset diabetes mellitus	48 (19.6)	40 (16.6)	NR	51 (20.8)	40 (16.5)	4.3 (2.6-11.2)
Lipid changes	58 (23.7)	23 (9.5)	2.48 (1.58-3.89)	66 (26.9)	28 (11.6)	15.4 (8.5- 22.2)
Infections	123 (50.2)	105 (43.6)	1.15 (0.95-1.39)	[redacted]	[redacted]	[redacted]
Renal failure	15 (6.1)	21 (8.7)	NR	[redacted]	[redacted]	[redacted]

CI, confidence interval; NR, not reported
EVR + rTAC, everolimus with reduced dose tacrolimus and corticosteroids
TAC control, tacrolimus with corticosteroids control arm
Adapted from European Public Assessment Reports published by the European Medicines Agency

4.36 The company reported that 74.3% of people in the trial tolerated everolimus in combination with reduced dose tacrolimus to month 12. No patients developed severe renal dysfunction (eGFR < 30 mL/min/1.73 m^2). The company commented that evidence from the network meta-analysis indicated that the treatments were comparable in terms of safety.

ERG comments

4.37 The ERG was satisfied with the company's approach to identifying studies reporting adverse events.

5 Cost-effectiveness evidence

Model structure

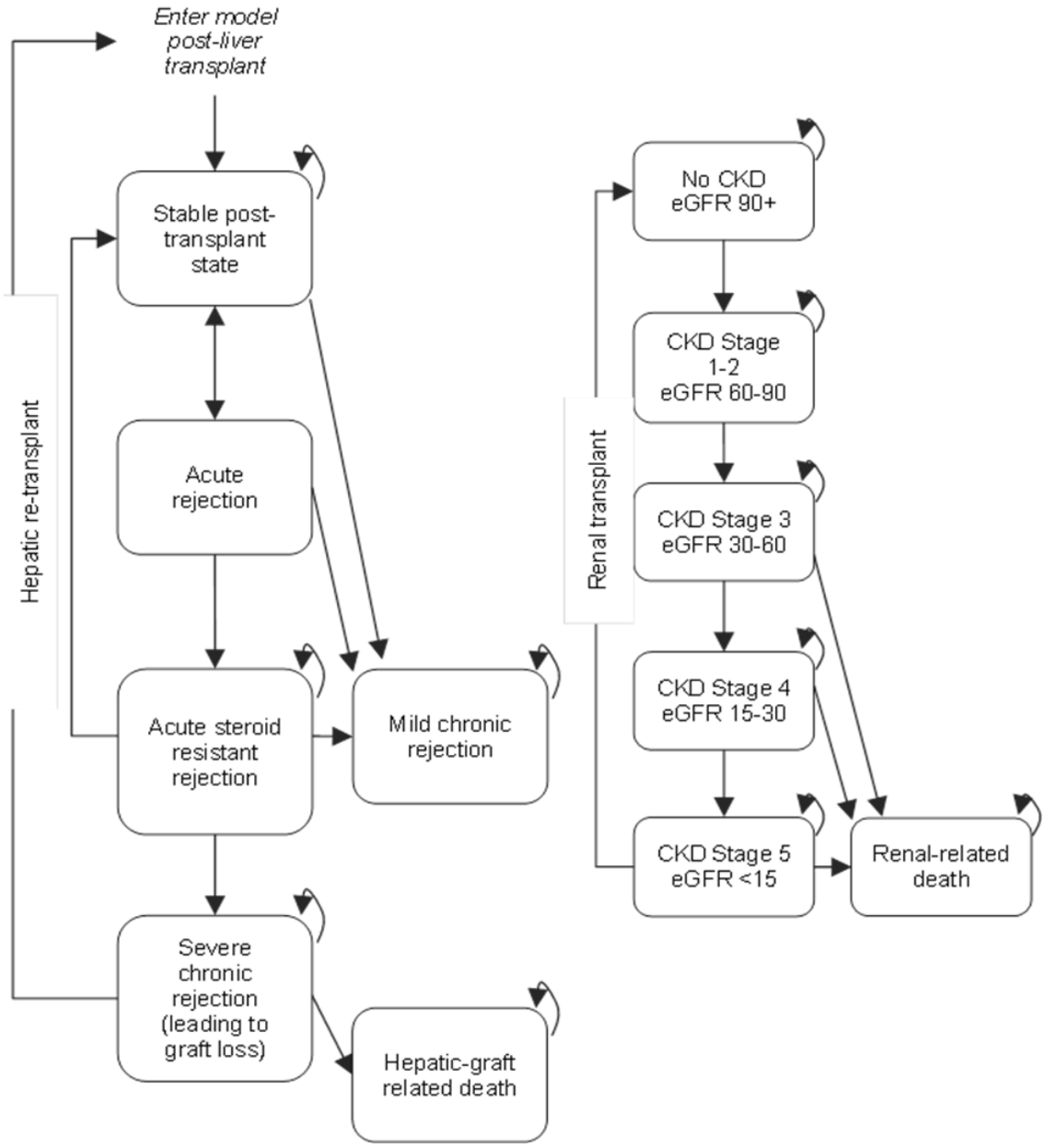
5.1 The company did not identify any existing cost-effectiveness analyses of everolimus in combination with reduced dose tacrolimus relevant to the decision problem.

5.2 The company developed a patient simulation model that evaluated the cost-effectiveness of everolimus in combination with reduced dose tacrolimus, with or without corticosteroids (that is people where assumed to have corticosteroids initially and then tapered off completely from 6 months onwards), compared with azathioprine or mycophenolate mofetil in combination with standard dose tacrolimus for maintenance immunosuppressive therapy. The model considered a hypothetical cohort of patients who had undergone a liver transplant for any reason. The model included a core hepatic rejection model and a renal sub-model. The company stated that the structure of the core hepatic rejection model was chosen following consideration of clinical guidelines for immunosuppression post-liver transplantation in the UK and existing clinical literature. The core model consisted of 6 health states: the 'stable post-transplant state', 'acute rejection', 'acute steroid resistant rejection', 'severe chronic rejection (leading to graft loss)', 'mild chronic rejection', and 'hepatic-graft related death'.

5.3 The company included the renal sub-model to demonstrate the 'renal sparing' effect of everolimus in combination with reduced dose tacrolimus. Health states in the renal sub-model were defined by the NICE clinical guideline on CKD progression. The sub-model included 5 health states defined by stages of chronic kidney disease (CKD), as measured by estimated glomerular filtration rate (eGFR).from no CKD (eGFR 90+) to CKD stage 5 (eGFR < 15). It also included a renal-related death state. Patients could also leave the model from natural (background) mortality.

5.4 The model had a lifetime time horizon (80 years) and a cycle length of 3 months, which the company stated reflected expert opinion that most acute rejection occurs after 3 months post transplantation. A half-cycle correction was not applied. The model used discount rates of 3.5% for costs and QALYs and an NHS/PSS perspective.

Figure 1. The company's model (descriptions of each health state are presented in table 45 and 46 of the company's submission)



ERG comments

5.5 The ERG considered that the company did not provide enough evidence to justify their approach in using a patient level simulation. The company reasoned that the use of a patient simulation model is appropriate when the patient flow is determined by time since last event or history of previous event. However, the ERG highlighted that only the 'Severe chronic rejection' state (SCR) was affected by time since last event, and

that the renal sub-model transition probabilities were not time dependent and also did not depend on history of previous events. Based on assessment of patient heterogeneity, and the patient baseline characteristics simulated in the economic model, the ERG considered that there was no need for a patient simulation model, and that a cohort state-transition model would have been more appropriate.

5.6 The ERG considered that more emphasis should have been placed on the renal component of the economic model but also that more interaction between the 2 models should have been considered (perhaps within one broader model structure). The ERG stated that this was because immunosuppressive therapy post liver transplantation has an impact on renal functioning but also, equally important, that renal functioning has an impact on graft survival.

5.7 The ERG found that the reporting of the model structure and its assumptions lacked clarity and that few justifications were provided for the assumptions used. In particular, the ERG questioned the clinical plausibility of the 'Mild chronic rejection' state (an asymptomatic state where it was assumed that patients could only move to this state 1 year post-transplant). The ERG's clinical expert adviser did not see a valid or justifiable reason for patients only to progress to this state 1 year after transplantation, therefore the relevance of including this health state in the model was not clear.

5.8 Clinical opinion provided by the ERG's clinical adviser was that 3-month cycles were too long to capture all the relevant events and that monthly cycles may have been more appropriate. The ERG also stated that because the cycle length of 3 months was relatively long, a half-cycle correction should have been applied. The ERG highlighted that although the impact of a half-cycle correction on the model outcomes would not be significant, no justification was given by the company as to why this wasn't applied.

5.9 The ERG considered that the time horizon of 80 years was unnecessarily high given that the average starting age of people in the model was 54 years. The ERG highlighted that after 40 years (when the average age in the model was 94 years), 100% of patients would have died.

5.10 The ERG was concerned with the number of simulations (10,000) and the lack of stability in the patient simulation model. The ERG's explored this in its exploratory analyses, see sections 5.42 and 5.43).

Model details

Transitions

5.11 In the core hepatic rejection model, disease progression from the 'Stable post-transplant' state to 'Acute rejection' was determined by the immunosuppressive regimen (the treatment arm). This probability of progression was derived from the probability of freedom from biopsy proven acute rejection (BPAR) at 3, 6 and 12 months for each treatment regimen, which was calculated from the network meta-analysis. The transition probabilities from the 'Stable post-transplant' state remained constant from the 5th cycle (starting at month 13) onwards. The absolute values used in the model for the progression from the 'Stable post-transplant' state for months 0 to 12 and beyond are presented in table 7. All other transition probabilities for the other health states were assumed to be constant and were therefore independent of the immunosuppressive regimen (these are presented in table 51 of the company's submission).

Table 7. Three month transition probabilities used in the base-case hepatic model for the 'Stable post-transplant' state (adapted from the company's response to clarification question B2).

Health state	To health state	EVR + rTAC	AZA	MMF	Assumption
First 3 months					
Stable post-transplant (SPT)	Stable post-transplant	98.1%	86.2%	88.7%	1 – P(leaving state)
	Acute rejection	1.9%	13.8%	11.3%	Probability constant over this 3 month period
Months 4 to 6					
Stable post-transplant (SPT)	Stable post-transplant	96.3%	92.5%	95.9%	1 - P(stable to AR) - P(stable to death)
	Acute rejection	3.7%	7.5%	4.1%	Probability constant over this 3 month period
Months 7 to 12					
Stable post-transplant (SPT)	Stable post-transplant	97.6%	98.5%	99.4%	1 – P(leaving state)
	Acute rejection	2.5%	1.6%	0.6%	Probability constant over this 3 month period
Month 13 onwards					
Stable post-transplant (SPT)	Stable post-transplant	96.6%	97.4%	98.4%	1 – P(leaving state)
	Acute rejection	2.5%	1.6%	0.6%	Probability constant over this 3 month period
	Mild chronic rejection	1.0%	1.0%	1.0%	Only after 12 months in state can this occur
Abbreviations: AZA, azathioprine; EVR, everolimus; MMF, mycophenolate mofetil; rTAC, reduced dose tacrolimus					

5.12 For the renal sub-model, transition probabilities for the first year were based upon the annual decrease in eGFR from baseline and were dependent on the treatment in year one. The relative difference between treatments was drawn from the network meta-analysis and used to derive the absolute eGFR decrease for each treatment (presented in table 8). After year 1, the company assumed that renal function followed a natural progressive decline meaning that transition probabilities were assumed to be constant. These transition probabilities were not time dependent or treatment arm dependent and were based on underlying disease progression probabilities (presented in table 48 of the company submission). Transition probabilities used in the renal sub-model are displayed in **Error! Reference source not found.** of the company's submission.

Table 8. Absolute eGFR decrease at 12 months used in the renal sub-model
(adapted from table 53 of the company's submission)

Event	Base case change in eGFR at 12 months ($mL/min^{-1}/1.73m^2$)	Low CI	High CI
Everolimus + reduced dose tacrolimus + corticosteroids	-23.1	-27.4	-18.7
Azathioprine + standard dose tacrolimus + corticosteroids	-31.6	-32.3	-30.9
Mycophenolate mofetil + standard dose tacrolimus + corticosteroids	-31.6	-32.3	-30.9

Utility values and health-related quality of life

5.13 Health-related quality of life data were not collected as part of the H2304 trial, therefore the company did a systematic literature review to identify health state utility values. The company identified 7 studies, 5 of which were studies eliciting EQ-5D in a UK population. Summaries of the identified studies are provided in table 57 of the company's submission. All of the studies provided data for patients post-transplant, but none of the studies provided utility data specific to either acute or mild rejection, nor did they report disutility data specific to adverse events. Utility scores for the health states in the hepatic rejection model and for the renal sub-model were based on Ratcliffe et al., 2002 and Neri et al., 2012 respectively, both UK studies using the EQ-5D instrument to elicit scores.

Table 9. Summary of utility values used in the company's cost-effectiveness analysis (adapted from table 26 of the ERG report)

State	Utility value	Reference in submission
Utility scores for health states in the main (hepatic rejection) model		
Stable post-transplant state	0.58	(Ratcliffe et al., 2002[136])
Acute rejection	0.58	(Ratcliffe et al., 2002[136])
Acute steroid resistant rejection	0.58	(Ratcliffe et al., 2002[136])
Mild chronic rejection	0.58	(Ratcliffe et al., 2002[136])
Graft loss (severe chronic rejection)	0.53	(Ratcliffe et al., 2002[136])
Stable post-transplant via liver re-transplant	0.58	(Ratcliffe et al., 2002[136])
Death	0	(EuroQol, 2009[152])
Utility scores for health states in the sub (renal sparing) model		
No CKD	0.83	Assumption
CKD stages 1 to 2	0.64	(Neri et al., 2012[134])
CKD stage 3	0.58	(Neri et al., 2012[134])
CKD stage 4	0.49	(Neri et al., 2012[134])
CKD stage 5	0.28	(Neri et al., 2012[134])
No CKD following renal transplant	0.81	(Liem et al., 2008[133])
Death	0	(EuroQol, 2009[152])
* The ERG found a mistake in the reporting of the 'severe chronic rejection' utility value. In the submission, a utility value of 0.43 is reported for this health state; however, the economic model uses a utility value of 0.53.		

5.14 Patients in the core hepatic model were assumed to have a stable health-related quality of life over time, with most states assuming an asymptomatic state where the utility value was 0.58. Patients in the more severe state of graft loss (severe chronic rejection) experienced a decrease in utility to 0.53. In the renal sub-model, patients' health-related quality of life decreased in line with their symptoms until renal transplant, from 0.83 in the 'No CKD' health state to 0.28 in the 'CKD stage 5' health state. The company used the 'minimum method', to take into account potential double counting of utility losses in simultaneous health states (for example hepatic rejection and renal dysfunction). The minimum method assumes that the lowest value is used as the estimate of joint state utility.

A summary of the health state utility values used in the company's economic model are presented in table 9.

Costs

Table 10. Drug costs used in the company's cost-effectiveness model

Regimen/drug	Cost per patient per day (starting dose)	Annual cost in Year 1 post-transplant
Everolimus regimen cost per cycle		**£9,084.89 per year**
Everolimus	£19.80 /day	£6,624.75 per year
Tacrolimus	£5.04 /day	£2,438.13 per year
Corticosteroid	£0.00 /day	£22.01 per year
Azathioprine regimen cost per cycle		**£3,967.22 per year**
Azathioprine	£0.08 /day	£28.00 per year
Tacrolimus	£8.51 /day	£3917.22 per year
Corticosteroid	£0.00 /day	£22.01 per year
MMF regimen cost per cycle		**£4,654.56 per year**
MMF intravenous	£0.00 /day	£512.12 per year
MMF oral	£1.16 /day	£203.21 per year
Tacrolimus	£8.51 /day	£3917.22 per year
Corticosteroid	£0.00 /day	£22.01 per year

5.15 In all regimens the tacrolimus dose was decreased over time as a patient's target blood trough levels changed. In the azathioprine and mycophenolate mofetil treatment arms of the model the mean daily dose of tacrolimus was 0.12 mg/kg reducing down to 0.07 mg/kg by month 9 onwards. In the everolimus arm of the model, the tacrolimus starting dose was [redacted] (see table 55 of the company's submission for further information).

5.16 The company obtained estimates of resource use for the hepatic rejection model from the University Hospitals Birmingham Foundation Trust and these were validated by the company's clinical advisers. For the renal sub-model, the company reported that NICE Clinical Guideline 182 and Kerr et al 2012 were the 2 sources used to obtain resource use data.

5.17 For the renal sub-model, all of the costs reported in the company's submission for the CKD health states were incorrect. The correct costs from the company's model were presented in table 33 of the ERG report.

Adverse events

5.18 The company estimated the occurrence of adverse events associated with the different treatment regimens based on the network meta-analysis and the summary of product characteristics for each drug product. These included hypertension, diabetes mellitus, infections, tremor and insomnia. A summary of the incidence of adverse included in the model events by treatment group is presented in table 11. The expected cost per treatment regimen was calculated by applying the cost of treating events with the probability of incurring the events. A summary of the costs associated with adverse events is presented in table 12. The disutility estimates for treatment related adverse events were estimated from the published literature where possible and are presented in table 58 of the company's submission.

Table 11. Incidence of adverse events used in the economic model (including disutility applied in the model).

Adverse event (disutility applied in the model)	**Everolimus with reduced tacrolimus**	**Azathioprine with standard tacrolimus**	**MMF with standard tacrolimus**
Hypertension (-0.04)	40.3%	57.8%	23.9%
New onset diabetes (-0.06)	15.7%	18.3%	11.6%
Infection (-0.01)	65.7%	60.3%	62.6%
Herpes (-0.001)	0.4%	5.9%	10.1%
Tremor (-0.003)	10.2%	35.5%	33.9%
Insomnia (-0.04)	6.9%	47.0%	52.3%
CMV (-0.01)	4.1%	8.0%	5.8%

Table 12 Adverse events cost data used in the economic model

Adverse event (disutility applied in the model)	Items	Treatment cost
Hypertension	Single treatment cost	£769
New onset diabetes	Single treatment cost	£1,840
Infection	Single treatment cost	£649
Herpes	GP visit	£55
Tremor	GP visit	£55
Insomnia	GP visit	£55
CMV (cytomegalovirus)	Single cost includes IV Ganciclovir IV, testing, imaging, hospital stay (14 days)	£11,365

ERG comments

5.19 The ERG questioned the validity and the applicability of the economic analysis within the NHS context because trough levels of reduced dose tacrolimus in the H2304 trial were above what would be considered as reduced levels in the UK clinical practice (see also section 4.9). It also highlighted that because the standard tacrolimus dose across the network meta-analysis studies was so heterogeneous, the network meta-analysis results that informed the model were likely to lack robustness (see also sections 4.30 and 4.31).

5.20 The ERG identified structural errors in the formulae allocating patients to different health states in the model which it considered could have been avoided if a cohort state-transition model had been used. The ERG could not correct these errors because of the computational burden of the running the patient-level simulation model, but it considered that the results were likely to be biased in favour of the everolimus treatment regimen.

5.21 The ERG commented that some patients started the renal sub-model model with negative levels of eGFR because of the random generation process used to estimate the baseline eGFR levels, and that this is not clinically plausible. The ERG explained that this meant they were immediately allocated to the CKD stage 5 category, where patients with a

negative eGFR level could stay for long periods of time (for example over 3 years) until they returned to CKD stages 1- 2 following a transplant.

5.22 The ERG noted that median survival in the model was achieved at around year 10, indicating considerable underestimation of survival in the model. It also highlighted that overall survival in the everolimus treatment regimen arm of study H2304 was 95% at 2 years whereas in the economic model only around 85% of patients were alive at the same point in time.

5.23 The ERG raised some concerns about the utility values used in the model. For example, it noted that the company had assumed that quality of life in the acute rejection and mild chronic rejection health states was the same as in the stable post-transplant state. However, clinical opinion sought by the ERG suggested that patients in the acute rejection and mild chronic rejection health states would require hospitalisation and that this would reduce their quality of life relative to the stable post-transplant state. The ERG also considered that the utility value of 0.83 for the 'no CKD' health state was more likely to represent CKD stage 1 and that the utility value of 0.64 for CKD stages1 to 2 was too low.

5.24 The ERG was generally satisfied with the sources used to obtain unit costs for the hepatic model. However, it highlighted that clinical practice varies across centres for liver transplantation patients but that the company obtained resource use data through 1 centre only and it was therefore important to validate these against different sources. In general, clinical opinion sought by the ERG disagreed with some of the resource data reported in the submission. The ERG commented that GP visits were unlikely to occur as frequently as described because most of these patients would be managed in secondary care. The ERG also highlighted that the number of tests required in some health states may be underestimated. For example, in the 'Stable post-transplant' state, people may also require a blood test to check immunosuppression trough levels. The ERG also considered that the cost associated with the mild chronic rejection health state (£640) seemed too high for an asymptomatic

condition that does not require treatment and was not clear why this was higher than the cost associated with the stable post-transplant health state (£73).

5.25 The ERG noted that the company used the most expensive brand price (£1.61 per mg) for tacrolimus (Prograf) in the economic model with no apparent justification. The ERG suggested that a weighted average price of £1.20 per mg (based on the market share information) for tacrolimus would have been more appropriate.

5.26 The ERG was generally satisfied with the estimation of adverse events and the quality of life data used to estimate these in the core hepatic rejection model. However, it did not agree that the costs and utility losses associated with everolimus-related adverse events should have been included for the 3 months in the first model cycle because everolimus therapy starts 1 month after surgery, and therefore the adverse events associated with the drug should have been considered only for 2 months.

Company's base-case results and sensitivity analysis

Table 13 Company's deterministic base-case results

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER vs baseline (£/QALYs)	ICER inc. (EVR vs AZA) (£/QALYs)
MMF + standard TAC*	£102,746	3.867	-	-	-	-
AZA + standard TAC	£105,529	4.022	£2,783	0.156	17,895	
EVR + reduced TAC	£140,750	4.210	£38,004	0.343	**110,797**	**187,842**

*Baseline is MMF + standard TAC
Abbreviations: AZA, azathioprine; EVR, everolimus; ICER, incremental cost-effectiveness ratio; LYG, life years gained; MMF, mycophenolate mofetil; QALYs, quality-adjusted life years; TAC, tacrolimus

5.27 Everolimus in combination with reduced dose tacrolimus was more costly and resulted in more QALYs than the other treatment regimens (see table

13). The deterministic base case incremental cost-effectiveness ratio (ICER) estimated by the company was £110,797 compared with mycophenolate mofetil in combination with standard dose tacrolimus (incremental costs £38,004, incremental QALYs 0.343) and £187,842 compared with azathioprine in combination with standard dose tacrolimus (incremental costs £35,221, incremental QALYs 0.188). The ICER for the azathioprine treatment regimen compared with the mycophenolate mofetil regimen was £17,895 per QALY gained.

5.28 No deterministic sensitivity analyses were reported in the company's submission. The company ran a probabilistic sensitivity analysis using 1000 simulations for 1000 patients. The company reported that the results of the probabilistic sensitivity analysis (see table 14) were similar to the deterministic base case results. The probabilistic ICERs for the everolimus treatment regimen were £105,526 and £184,714 compared with the mycophenolate mofetil and azathioprine treatment regimens respectively. The ICER for the azathioprine treatment regimen compared with the mycophenolate mofetil regimen was £13,762 per QALY gained. The company also reported that a test of 2000 simulations by 5000 patients gave similar results.

Table 14. Company's probabilistic sensitivity analysis with mycophenolate mofetil as the baseline therapy

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£) vs baseline (QALYs)	ICER (£) inc. (EVR vs AZA) (QALYs)
MMF + standard TAC*	104,240	4.945	-	-	-	-
AZA + standard TAC	106,384	5.101	2,145	0.156	13,762	-
EVR + reduced TAC	139,746	5.281	35,506	0.336	**105,526**	**184,714**
*Baseline is MMF + standard TAC; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

5.29 The company presented a scatterplot from the probabilistic sensitivity analysis (see figure 14 of the company's submission) which indicated that for all simulations the ICER for the everolimus treatment regimen compared with the mycophenolate mofetil regimen was higher than £30,000 per QALY gained. Similarly, the majority of points on the scatterplot (>99%) were above £30,000 per QALY gained for the comparison of the everolimus and azathioprine treatment regimens.

5.30 The company presented a cost-effectiveness acceptability curve (see figure 15 of the company's submission) which indicated that everolimus in combination with reduced dose tacrolimus was likely to be the most cost effective therapy at thresholds over £200,000 per QALY gained.

5.31 The company highlighted that the key drivers of the cost-effectiveness results were time to BPAR because the risk of acute rejection determined whether or not a patient became at risk of developing chronic rejection and potential loss of the graft. It also highlighted that the complications of immunosuppressive treatment as modelled in the renal sub-model had a large impact on results. The magnitude of the decline in renal function in year 1 followed by the progression of CKD had a large impact on the cost-effectiveness analysis.

ERG comments

5.32 The ERG noted the company's explanation for the high base-case ICERs that the treatment regimens have similar high efficacy and that everolimus is a branded product being compared with generic comparators.

5.33 The ERG noted a serious logical error in the model when analysing data provided by the company on the average number of cycles spent in the different health states of the model. It noted that there were a total of 320 cycles in the model and that in the hepatic rejection model patients spent an average of 41 cycles in the everolimus in combination with reduced dose tacrolimus arm. In the remaining 279 cycles the patients were dead. However, in the renal model, patients only spent 31 cycles alive in the

model, meaning that 10 cycles were "missing" from the renal sub-model. The ERG suggested that this logical error reflected a problem in the model formulae and/or structure.

5.34 The ERG commented that it would be useful to understand what the key drivers of the economic model were, especially considering the high ICERs presented, but that this was not possible because the company did not undertake deterministic sensitivity analysis.

5.35 The ERG highlighted that the results of the probabilistic sensitivity analysis were based on a small number of simulations (1000) and was unlikely to have generated reliable estimates.

Company scenarios

5.36 The company undertook the following scenario analyses:

- Scenario 1: Removing the 'Mild chronic rejection' state
- Scenario 2: Removing the possibility of future transplants (in both models)
- Scenario 3: Removing the renal sub-model
- Scenario 4: Changing the baseline eGFR from 81ml/min per 1.73m^2 to 60 ml/min per 1.73m^2

The results of these scenario analyses are presented in table 15.

Table 15 Scenario analyses (adapted from table 76-79 of the company's submission)

Scenario	**Total cost**	**Total QALY**	**Inc. cost**	**Inc. QALY**	**ICER** (£/QALY)	**Incremental ICER** (£/QALY)
Scenario 1- removal of 'mild chronic rejection' state						
MMF + standard TAC*	102,856	4.09				
AZA + standard TAC	104,907	4.05	2,051	-0.04	**Dominated**	**-**
EVR + reduced TAC	140,189	4.25	37,333	0.16	**227,528**	**-**
Scenario 2 – removal of the possibility of future transplants						
MMF + standard TAC	119,924	3.45				
AZA + standard TAC	122,468	3.46	2,544	0.01	**Extendedly dominated**	**-**
EVR + reduced TAC	149,418	3.69	29,494	0.24	**121,972**	**117,285**

Scenario 3- removal of renal sub-model						
MMF + standard TAC	43,666	4.10				
AZA + standard TAC	45,679	4.13	2,103	0.03	**73,175**	**-**
EVR + reduced TAC	85,095	4.24	41,429	0.13	**312,279**	**374,832**
Scenario 4 – Changing baseline eGFR from 81ml/min per 1.73m2 to 60 ml/min per 1.73m2						
MMF + standard TAC	129,448	3.62				
AZA + standard TAC	131,392	3.63	1,943	0.01	**Extendedly dominated**	-
EVR + reduced TAC	160,845	3.79	31,396	0.17	**184,327**	**179,427**
Abbreviations: Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio; MMF, mycophenolate mofetil; TAC, tacrolimus; AZA, azathioprine; EVR, everolimus.						

5.37 In scenario 1, the removal of the 'mild chronic rejection' state increased the ICER for everolimus in combination with reduced dose tacrolimus to £227,528 compared with mycophenolate mofetil in combination with standard dose tacrolimus. The azathioprine treatment regimen was dominated by the mycophenolate mofetil regimen.

5.38 In scenario 2, the removal of the opportunity for re-transplant resulted in an ICER for everolimus in combination with reduced dose tacrolimus of £121,972 compared with the mycophenolate mofetil treatment regimen and £117,285 compared with the azathioprine treatment regimen.

5.39 In scenario 3, the removal of the renal sub-model increased the ICER for everolimus in combination with reduced dose tacrolimus to £312,279 compared with the mycophenolate mofetil treatment regimen and to £374,832 compared with the azathioprine treatment regimen. The company stated that the large impact on the results reflected the benefit that the everolimus treatment regimen provides for patients through a renal sparing effect.

5.40 In scenario 4, the reduction of baseline eGFR resulted in an ICER for everolimus in combination with reduced dose tacrolimus of £184,372 compared with the mycophenolate mofetil treatment regimen and £179,427 compared with the azathioprine treatment regimen. The

company highlighted that the results of the scenario analyses demonstrated that the model was sensitive to changes in baseline eGFR.

ERG comments

5.41 The ERG could not find a plausible reason why removing the 'Mild chronic rejection' state increased the ICER for the everolimus treatment regimen compared with the mycophenolate mofetil regimen but decreased it compared with the azathioprine regimen. The ERG questioned the clinical validity of the 'Mild chronic rejection' state but also the assumptions made by the company with regards to the resource use in this state (see also section 5.24).

ERG exploratory analyses

5.42 The ERG ran 2 iterations of the company's base case model using the same number of simulations and the same assumptions**,** to test the model's stability with regard to the ICER results. The ERG found considerable variation in the ICERs reported, especially for the everolimus treatment regimen compared with the mycophenolate mofetil regimen, with the ICERs ranging from £110,797 to £120,651 (nearly a 9% change). The ERG concluded that it was extremely concerned about the lack of stability in the base case ICERs.

5.43 The ERG tried to determine the cause of instability in the model results. Therefore it "fixed" the baseline characteristics of patients (by taking their mean values) in the simulation model instead of allowing these values to vary each simulation according to a distribution. The reason for this analysis was to understand if the variation in results was generated by the simulated patient characteristics or if it was attributable to other problems in the model. The results of this exercise generated ICERs for the everolimus treatment regimen compared with the azathioprine regimen that ranged from dominant to £797,558 per QALY gained. For the everolimus treatment regimen compared with the mycophenolate mofetil regimen, the ICERs ranged from £431,348 to £582,668 per QALY gained.

The ERG therefore considered that the instability of the model could not be solved by fixing patient baseline characteristics as mean estimates.

5.44 The ERG lacked confidence in the ICERs presented by the company but it considered that it would not be helpful to run any additional analyses with different input values because of the instability of the results. The ERG stated that it could not therefore make any predictions regarding the true cost effectiveness of everolimus.

Innovation

5.45 Justifications for considering everolimus to be innovative:

- The company stated that while use of calcineurin inhibitors is important in reducing acute rejection, supported by proven effectiveness, there is an urgent need to reduce the related complications of calcineurin inhibitors including nephrotoxicity in liver transplantation patients.
- The company highlight that because of limitations of available evidence, some aspects of the innovative nature of everolimus may not have been captured in the cost-effectiveness model, particularly the impact of everolimus on the recurrence of hepatocellular carcinoma. In addition, the feasibility of modelling complex long-term complications such as diabetes mellitus and cardiovascular disease could mean the QALY calculation does not fully consider these events
- The company stated that naïve comparison data for outcomes such as recurrence of hepatocellular carcinoma have been presented in the submission from the pivotal registration trial H2304, for which 36-month data are available compared with more limited data for the relevant comparators.

6 Equality issues

6.1 No equality issues were raised during the scoping consultation or in any of the submissions from the company, patient groups or clinical experts.

7 Authors

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Appendix A: Summary of product characteristics

Everolimus 0.1 mg, 0.25 mg dispersible tablets, 0.1 mg, 0.25 mg, 0.5 mg, 0.75 mg and 1.0 mg tablets.

http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/index.htm?subsName=EVEROLIMUS&pageID=SecondLevel