Decision Problem
The scope of the appraisal described the comparator as standard immunosuppressive therapy with a calcineurin inhibitor (such as tacrolimus or ciclosporin) and a corticosteroid in combination with azathioprine or mycophenolic acid.

A1. **Priority Question**: The Company submission has excluded ciclosporin from the analysis as "clinical practice for post-liver transplant immunosuppression in the UK is based on tacrolimus combination regimens". However, this is not consistent throughout the submission. For example, both sets of PICOS criteria in Table 14 and Table 15 include ciclosporin. Therefore please clarify your strategy with regards to ciclosporin.

Ciclosporin monotherapy was excluded from all of the searches because as stated in section 6.7.1, this therapy option is rarely used in UK clinical practice.

There is an omission in the statement of the decision problem which should have clarified that combination therapies (ciclosporin or tacrolimus) were included as comparators for the clinical searches. The study eligibility criteria for the NMA were designed to be broad enough to capture a wide range of potential comparators as required by the final NICE scope. The comparator decision problem addressed in the submission should have included this before the sentence starting 'Tacrolimus in combination with azathioprine or mycophenolate mofetil with or without corticosteroids.'

Following abstract review, consultation with clinical experts and review of the outputs, it was determined that interventions containing tacrolimus were of primary interest to UK clinical practice. The model therefore addressed this specific combination (tacrolimus in combination with azathioprine or mycophenolate mofetil with or without corticosteroids) for the estimates of cost-effectiveness.

The sentence in Section 5 of the Comparator(s) cell for the column that reads 'Decision problem addressed in the submission' on page 36 should read:

"Combination therapies (ciclosporin or tacrolimus) were included as comparators for the clinical searches within the submission. Following abstract review, consultation with clinical experts and review of the outputs, it was determined that interventions containing tacrolimus were of primary interest to UK clinical practice. The model therefore addressed this specifically tacrolimus in combination with azathioprine or mycophenolate mofetil with or without corticosteroids for the estimates of cost-effectiveness."

A2. **Priority Question.** The Company submission includes evidence for the other comparator drugs both with and without corticosteroids. However there is limited about which studies included in the analysis (NMA) used corticosteroids. Please provide details about the use of corticosteroids in the NMA studies and the economic analysis. The results presented (section 7) do not make any references to corticosteroids in the intervention or comparator arms of the model.

All trials used in the NMA included the use of corticosteroids. However, clinical practice on corticosteroid use tends to vary and trials tend to specify

corticosteroid usage as per local centre use (e.g. H2304, Nashan 2009 etc.). In H2304 (Table R1), steroid withdrawal was not permitted until 6 months. The table below provides details on which trials included steroids as reported in the publications, but this information should be interpreted with the above background in mind. As all clinical studies have included the use of corticosteroids, any clinical data used in the model from the NMA or from the clinical trial included the use of corticosteroids. However, the studies that were used to populate the cost and utility information in section 7 were not based on hepatic immunosuppression trial information and therefore did not include information about corticosteroid use in the text.

Table R1: Corticosteroid dosage by study included in the NMA

Number	Name	Year	Dose
1	(de Simone *et al.*, 2012[1])	2012	5 mg/kg
2	(Garcia-Gonzalez *et al.*, 2005[2])	2005	5 mg/kg
3	(Neuberger *et al.*, 2007[3])	2007	NR
4	(Klintmalm *et al.*, 2011[4])	2011	The dosage was orally tapered to 10 mg/day by day 30 and to 5 mg/day by day 90
5	(Boillot *et al.*, 2001[5])	2001	3 month cohort, dual therapy - 2.562 - 0.233 mg/kg triple therapy - 2.312 - 0.234 mg/kg. 12 month cohort, dual therapy 0.190 - 0.132 triple therapy - 0.294 - 0.120
6	(Fisher *et al.*, 1998[6])	1998	NR
7	(Jain *et al.*, 2002[7])	2002	1 g of methylprednisolone on reperfusion of the liver and a 6-day methylprednisolone taper thereafter, starting at 200 mg/d and ending at a baseline dose of 20 mg/d.
8	(Junge *et al.*, 2005[8])	2005	10 to 20 mg/d)
9	(Wiesner *et al.*, 2001[9])	2001	NR
10	(Nashan *et al.*, 2009[10])	2009	NR
11	(Greig *et al.*, 2003[11])	2003	1.0 mg/kg/d on day 1, 0.8 mg/kg/d on day 2, 0.6 mg/kg/d on day 3, 0.4 mg/kg/d on day 4, and 0.3 mg/kg/d (usually 20 mg/d) thereafter during month 1; 0.2 mg/kg/d (usually 15 mg/d) during month 2; and 0.15 mg/kg/d (usually 10 mg/d) during month 3.
12	(Marin Gomez *et al.*, 2011[12])	2011	NR
13	(Neuhaus *et al.*, 1997[13])	1997	5 mg/kg
14	(Boudjema *et al.*, 2011[14])	2011	20 – 15 mg for the first 6 weeks, 15–10 mg from week 7 to 12 and 10–0mg from month 4 to 6.
15	(Takada *et al.*, 2013[15])	2013	1 mg/kg/day on days 1 to 3 to 0.5 mg/kg/day on days 4 to 6 and to 0.3 mg/kg/day on day 7
16	(Dmitrewski *et al.*, 1994[16])	1994	induction dose of 1 g methylprednisolone followed by 20 mg/day prednisolone.
17	(Porayko *et al.*, 1994[17])	1994	Methylprednisolone 1g on 2 consecutive days, followed by a prednisone recycle with a rapidly tapered dosage 200mg to 20mg during the next 6 days
18	(Therapondos *et al.*, 2002[18])	2002	NR
19	(Salizzoni *et al.*, 2001[19])	2001	1000 mg IV methylprednisolone intraoperatively. Thereafter, oral prednisolone was tapered from 15 to 20 mg/d (month 1) to 10 to 15 mg/d (month 2) and 5 to 10 mg/kg (month 3).

20	(Manousou *et al.*, 2009[20])	2009	16 mg/day intravenously) was given until oral intake was established; then, 20 mg/day prednisolone was used
21	(Samonakis *et al.*, 2006[21])	2006	Methylprednisolone (16mg/day IV) until oral intake was established, when 20mg/day prednisolone was used
22	(McDiarmid *et al.*, 1993[22])	1993	Methylprednisolone 0.3 mg/kg/day, methylprednisolone 200 rag/day tapered to 0.3 mg/kg/day by day 6

A3. **Priority Question.** The Company submission states that 'mycophenolate mofetil is specified in the submission as mycophenolate sodium' but this expression has not been included as a search term. Please confirm why this term has been omitted. If it has been excluded by mistake, please repeat the searches to include this term, highlighting any additional studies which are identified and any additional studies which meet the inclusion criteria.

Page 36 of the submission highlights that only mycophenolate mofetil has been included as a comparator. As noted there are two available presentations of mycophenolic acid - mycophenolate mofetil (Cellcept®, generics) and mycophenolate sodium (Myfortic®). The full sentence referred to in the question above is 'Mycophenolate mofetil is specified in the submission as mycophenolate sodium (an alternate presentation of mycophenolic acid) does not have a license in liver transplantation.' As stated, mycophenolate sodium is not licensed for use in liver transplantation (section 4.1 http://www.medicines.org.uk/emc/medicine/14917) but only in renal transplantation. Therefore only trials investigating mycophenolate mofetil were included in the evidence synthesis, hence why the submission sought to highlight why mycophenolate sodium was not included as a search term in any of the searches conducted.

Clinical Evidence

A4. **Priority Question.** On page 41 of the submission, Table 4, it seems that the inclusion criteria for the comparator section is missing from the cell on second column, second row. Please provide this missing information. Also please confirm if the decision to exclude graft function/fibrosis and time to recurrence of hepatocellular carcinoma was solely based on expert opinion or if any searches regarding these outcomes were undertaken beforehand.

The clinical search included all relevant comparators (azathioprine and MMF in combination either with tacrolimus or ciclopsorin with or without corticosteroids), with the aim of first RCT search to find data relevant to the intervention everolimus in combination with reduced dose tacrolimus (with or without corticosteroids). Therefore the stated comparators were not included in the table referred to in the question, however, for completeness, the comparators are included below. A further typographical error was spotted whilst updating the PICOS criteria. Hepatocellular carcinoma was in the inclusion criteria, but the justification states that it was excluded. Hepatocellular carcinoma was not excluded as an outcome in the search. However, after a feasibility analysis was conducted for this outcome to be included in an NMA, it was not possible to make a network for this outcome.

Graft function/fibrosis, however, was excluded based solely on expert opinion within the UK, though it should be noted that no papers were excluded based on containing information on this outcome. No additional searches were undertaken beforehand.

Table R2: Revised PICOS criteria including comparators

Criteria	Inclusion criteria	Exclusion criteria	Justification
Population	Adults on maintenance immunosuppressive therapy following allogeneic liver transplantation.	• Any non-liver related transplant patients. • Pre-liver transplant patients including induction therapy. • Non-human. • Paediatric.	The expected license for everolimus is in combination with reduced dose tacrolimus as 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.
Intervention/ Comparators	Everolimus in combination with reduced dose tacrolimus with or without corticosteroids. Azathioprine or MMF in combination with a calcineurin inhibitor (ciclosporin or tacrolimus) with or without corticosteroids	• Sirolimus regimens. • Any regimen in combination with an induction treatment. • Any study without information on dosages.	• 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 in immunosuppressive regimens depending on patient response in order to reduce the risks of long-term adverse events associated with corticosteroid use. Therefore studies with or without corticosteroids were included to take into account clinical practice.
Outcomes	• Patient survival; • Graft survival; • Time to acute rejection; • Renal function; • Time to end-stage renal disease; • Time to recurrence of hepatocellular carcinoma; • Adverse effects of treatment; • HRQL.	• Studies that do not focus rejection of the liver as an outcome (efficacy) or HRQL. • Studies with only cost and no clinical outcomes.	These include all the outcomes derived from the final scope issued by NICE, except for the following: • Graft function / fibrosis • Expert opinion advised that in clinical experience there was limited evidence to differentiate between interventions with regard to graft function/fibrosis.
Study design	• RCTs of any duration, including cross-over RCTs if data were presented at cross-over. • Studies published as abstracts or conference presentations were	• Non-RCT study designs or articles reporting results of RCTs published elsewhere, e.g. reviews, meta-analyses/pooled	• Only RCTs were considered in line with the objective of this literature search.

	eligible for the primary analysis of clinical effectiveness if adequate data are provided.	analyses, editorials, notes, comments or letters.	

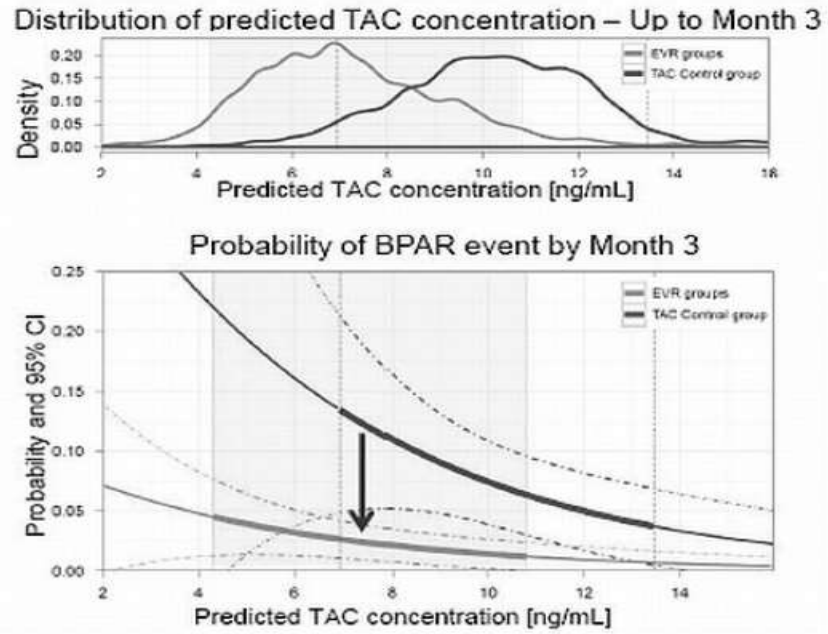
A5. Table 7 on page 48 of the Company submission presents the excluded studies. It would be useful to have a brief summary of study results (in terms of efficacy and adverse events for example), particularly the ones with relevance to the decision problem like T2304, which considers everolimus with reduced dose of tacrolimus.

As noted in Table 7, only two excluded studies consider everolimus in combination with reduced dose tacrolimus. Of these, one is still an ongoing study (H2307, (Song *et al.*, 2013[23])) with no data available. The reference to 'T2304' is a typographical error- this should say H2304. The two studies (Junge et al 2013[43], Junge et al 2013[44]) referred to here, look at H2304 data up to 12 months in order to investigate the relative potency of everolimus and tacrolimus, and the probability of acute rejection at the same tacrolimus blood concentration between treatment arms in H2304. These data are not relevant to the decision problem but the results are provided below for information:

	TAC Control		EVR + reduced TAC			
ENDPOINT	N	Mean TAC Conc [ng/mL]	N	Mean TAC Conc [ng/mL]	Mean EVR Conc [ng/mL]	Relative Potency of EVR
No Infection	133	8.9	122	5.6	5.3	0.64
No Serious infection	213	8.8	195	5.5	5.4	0.60
EPIOIS 1	98	8.9	102	5.4	5.2	0.69
EPIOIS 2	160	8.7	161	5.4	5.4	0.62

TAC, tacrolimus; EVR, everolimus; r, reduced; N, number.

Taken from Junge et al, How to Dose for Effective/Safe CNI Reduction? Transplantation Proceedings. 2013;45:1979-80.



Taken from Junge et al, Everolimus (RAD001) treatment effect in liver transplantation-a rational approach to quantify the mTOR effect. American Journal of Transplantation. 2013;13:504-5.

As noted, the first study determines the relative potency of everolimus dose compared to tacrolimus dosing in cohorts in the two trial arms that could be similarly grouped by outcomes. The second study showed that the probability of BPAR was lower for a given tacrolimus concentration in the everolimus arm as compared to the standard tacrolimus arm. At month 3, this hazard ratio was 5.37 (95%CI 2.14, 13.50, p <0.001). Similar consistent results were found for other endpoints at month 3 and all endpoints at 12 months, but were not presented in the published abstract.

A6. **Priority Question.** On page 49 of the Company submission it states that "*The patients in the Tacrolimus elimination arm who had not reached Day 180 post-randomisation were discontinued from the assigned study treatment and switched to local standard treatment".* On page 59, the submission subsequently states that these patients "*were expected to be converted to local standard treatment and to enter the follow-up phase".* Please provide more detail as to how these patients (n=231) were dealt with in the analysis. Have they joined the comparator arm of the trial (tacrolimus/prednisolone) and if so, were there any statistical analyses/adjustments to account for this? Also, what is the period referred to as follow-up phase?

All patients who discontinued study medication prior to the 24 month time point had post-study follow-up contact made at the protocol visits scheduled for months 3, 6, 9, 12, 18 and 24 (except in patients who prematurely discontinued medication due to death, lost to follow-up, administrative problems, withdrawal of consent by patient or graft loss). This 'follow-up period' is what is referred to on page 59 of the submission. Patients who discontinued study medication due to the Data Monitoring Committee decision on the tacrolimus elimination arm entered this follow-up phase after conversion to local standard treatment of care. At these follow-up visits, information was collected on vital signs, hospitalizations, rejection episodes, central laboratory samples, SAEs, graft loss / re-transplant etc. These patients did not join the comparator arm of the trial so no statistical analyses or adjustments were needed.

A7. **Priority Question.** Page 51 of the Company submission states that patients were randomised into the H2304 study 30 days after transplantation. Please confirm whether this in line with other trials included in the NMA as this could bias the results.

No other trials included in the NMA randomised patients at 30 days after transplantation as seen in H2304. Feasibility and dose finding studies for everolimus focused on conversion from calcineurin inhibitors to everolimus. It was postulated that early conversion from CNI would limit potential nephrotoxic adverse events of CNIs more effectively than later conversion. Therefore H2304 was designed to investigate early conversion to everolimus via elimination or dose reduction of tacrolimus. The nature of the trial design therefore required the 30 day run-in period prior to randomization- essentially stable post-transplant patients were converted to an everolimus containing regimen or maintained tacrolimus based standard of care.

Comparator trials will therefore by definition not have such a trial design unless they are similarly investigating conversion between immunosuppressive regimens. All other trials began therapy immediately

post-transplant. No NMA could have been conducted if only trials that shared a similar design were considered for inclusion- in which case, only the evidence elicited from H2304 would have been used to inform the submission. As the run-in period was relatively short and only stable post-transplant patients were considered for inclusion, it is unlikely that significant bias was present given particularly when a 12 month trial time horizon was considered.

A8. **Priority Question.** For Tables 9 and 10 on pages 66-69 of the submission, please explain why the numbers for deaths and graft losses do not match the numbers in Figures 4 and 5 respectively (pages 61-62) for either of the treatment arms. Please also explain why the reporting of adverse events in Figures 4 and 5 is not consistent with Table 43. In addition, the face validity of the p-value<0.001 for the Kaplan–Meier composite efficacy survival probabilities in Table 9 is questionable when confidence intervals (CIs) include 0. Please explain this.

The numbers for deaths and graft losses in Figures 4 and 5 correspond to the reasons for discontinuation, and therefore do not include the total number of events experienced. Similarly, the adverse events recorded in Figures 4 and 5 correspond to the reasons for discontinuation and not all those who experience adverse events discontinue the study so therefore, the numbers will differ.

The p-value reported in the submission is for the non-inferiority of everolimus plus reduced tacrolimus versus standard tacrolimus. The p-value can be significant for a test of non-inferiority measurement even if the confidence intervals cross zero. The difference test for superiority for the same outcome had a p-value of 0.292.

A9. **Priority Question.** On page 68 of the submission there is no information on the availability of the p-value for severity of rejection, HCC outcome and HCV recurrence. Please clarify this.

There is no p-value information for severity of rejection as there were no events in the everolimus arm and therefore it was not possible to calculate a p-value. For the HCC outcome and HCV recurrence, the numbers presented are absolute values and no statistical comparison was reported.

A10. **Priority Question.** On page 70, the Company submission presents the subgroup baseline results. Please provide some clinical interpretation of the results.

Patients entering H2304 were stratified by HCV status and stratum of renal function. Tables 11, 12 and 13 report 12 and 24 month data report the incidence rates in the primary composite endpoint and change in renal function as measured by eGFR. As these sub-groups were not powered to demonstrate differences between the treatment arms, the results may have limited clinical value. With regard to the demographic strata in respect of the primary composite endpoint, there appears to be little difference between the everolimus arm and the tacrolimus control arm. Absolute incidence numbers of the primary endpoint were low in both trial arms therefore further clinical interpretation of these results may have limited value.

Similarly, composite primary endpoint incidence for stratified HCV status and renal function groups show no significant difference between trial arms, although there is a general trend for incidence rates to be numerically in favour of the everolimus arm. Again, absolute incidence numbers were generally low in both arms, offering little scope for further clinical interpretation. Lastly, sub-group analysis is presented with respect to mean change in renal function (eGFR). No detailed statistical analysis is available and it is not possible to draw firm clinical conclusions from the sub-group

outputs, apart from the general observation that the everolimus arm tends to demonstrate a degree of preservation of renal function (i.e. a smaller reduction in mean eGFR).

A11. **Priority Question.** The ERG believes that Section 6.7 would benefit from the inclusion of summary tables to synthesise raw data, further description of the methods used to undertake NMA and more detailed interpretation of results. Please provide this information. More specifically, we would like to make reference to Jansen et al, 2011 (submitted by the Company) and the simplified checklist of items to be included in a report of meta-analysis presented in the paper (Table 1) as a reference of what should be included/updated in the manufacturer submission.

The data in section 6.7 are presented in tabular format in the appendix of the original submission (Section 10.14.2). Table R3 presents the Jansen (Jansen *et al.*, 2011[24]) checklist and where to find this information within the submission and/or clarification questions.

Patient characteristics

The patient characteristics extracted from each included RCT are shown in Appendix 10.14.2 of the submission. The characteristics include age, gender, BMI, the proportion of patients with HCV and HCC, kidney function measured by eGFR using any formula or by eCCR. The prevalence of diabetes and hypertension were also extracted, as well as donor age and cold ischemic time of the donor organ.

A full description of the patient characteristics data and any variations is presented in section 6.7.3 of the submission.

Time to event outcomes

The overall survival data used in the NMA are presented in Appendix 10.14.2 of the submission. The denominators (ITT population) and the KM probabilities are reported in the individual studies. The numerators (number of patients still alive) are calculated by multiplying the KM probabilities by their corresponding denominators. Some KM probabilities have been extracted from figures using the Digitizeit software. In this case, the symbol $ is reported next to the value in Appendix 10.14.2 in the submission. Only studies reporting overall survival data at 12 and/or at 24 months are present in this table. The other studies identified by the SLR did not report data on these two outcomes.

It should be noted that these data are not utilised in the economic model as mortality in the model is considered a function of hepatic graft loss and/or renal function. However, the model estimates are generally in line with the data found in the literature.

Adverse events

The denominators (ITT population for withdrawals due to AEs and safety population for AEs) were reported in the individual studies, except in HCV-3 (Klintmalm *et al.*, 2007[25]). In this study the number of patients experiencing the events and the corresponding proportions were reported. For each AE, the denominators were calculated by dividing the number of patients experiencing

the events by the proportions of patients reported to have experienced the event. For all other studies, the proportions of patients experiencing the event were calculated by dividing the numbers of patients experiencing the event by the corresponding denominators.

Table R3: NMA checklist by Jansen et al

Checklist Item	Brief explanation	Where to find full description in submission/clarification questions
Rationale for the study and study objectives	Identify evidence for immunosuppressive therapy for liver transplant	Section A – Decision problem
Description of eligibility criteria	Conducted in accordance with CRD guidelines and PRISMA	Submission – Table 14 and 15
Information sources	Online databases, clinical trial registries, and conferences	Submission – Section 6.1
Search strategy	Inclusive of all relevant disease terms and comparators	Submission – Section 6.1 and Section 10.2 appendix 2
Study selection process	Double screening at abstract and full text	Submission - Section 6.2
Data extraction	Key study design, patient characteristics, efficacy and safety outcomes were extracted by one reviewer, checked by another	Submission – Section 6.3
Validity/quality assessment	NICE checklist used for the assessment of risk of bias	Submission – Section 6.4 and section 10.3 Appendix 3
Outcome measures	Key clinical and safety outcomes (e.g. OS, Graft survival, renal function, withdrawals, hypertension, HCV, HCC)	Submission – Section 6.5
Description of methods used for analysis/synthesis of evidence	Fixed and Random effects models without covariate interactions due to paucity of data	Submission – Section 6.7.1
Description of analyses methods/models; Analysis Framework	Bayesian approach and explanation provided.	Submission – Section 6.7.4
Handling of potential bias/inconsistency	Feasibility analysis to identify viable networks and sources of bias; Covariate analysis was attempted but not possible; Extensive scenario analysis was conducted; Inconsistency models run.	Submission – Section 6.7.1, Section 6.7.6
Sensitivity analyses	Scenario analyses; Vague priors were used in line with NICE DSU guidance ($\sigma \sim$ Uniform(0,5) for between trial analysis.	Submission – Section 6.7.1
Do the results include a summary of the studies included in the network of evidence	Summary of study identification and selection presented.	Submission – Appendix 10.14.2
Individual study data	Description of study design, patient characteristics and outcomes are given	Submission – Section 6.7.3 and Appendix 10.14.2

Network of studies	Yes, all networks are presented where feasible.	Submission – Appendix 10.14.1
Does the study describe an assessment of model fit? Are competing models being compared?	Yes, DIC and posterior mean distribution scores are presented and where close, both models are presented	Clarification questions – A16
Are the results of the evidence synthesis presented clearly?	Tables presenting all pairwise comparisons, point estimates, uncertainty (CrI) and inconsistency are presented for each outcome	Submission – Section 6.7.5
Sensitivity/scenario analyses	Various scenario analyses were performed and are presented	Submission – Section 6.7.7
Description/summary of main findings	Discussion of NMA findings, limitations and generalizability is presented	Submission – Section 6.10.2
Internal validity analysis	Consistency is discussed.	Submission – Section 10.3, Appendix 10.3
External validity	Generalizability is discussed.	Submission – Section 10.3
Implications for target audience	Interpretation of results from a clinical perspective is presented.	Clarification questions – A11, A12, A13, A17, Submission – Section 6.10

A12. **Priority Question.** Please provide further justification regarding the choice of the clinical endpoints/outcomes considered for the NMA.

The clinical endpoints / outcomes included in the network meta-analysis were selected on the following basis:

- Relevant key efficacy outcomes with regard to immunosuppressive treatment regimens e.g. graft survival, acute rejection, overall survival. These outcomes were reflective of the primary composite endpoint of H2304 and relevant to all comparator trials that may have been included in the network meta-analysis.
- Renal function was included as a key aspect of the clinical rationale of H2304 and the use of everolimus in immunosuppression is the potential preservation of renal function through the minimization of CNI (tacrolimus / ciclosporin) dose.
- Safety outcomes were selected with reference to previous clinical trials in hepatic immunosuppression and confirmed to be of relevance via clinical expert advice. Recurrence of hepato-cellular carcinoma and new onset / recurrence of HCV infection are known issues of importance in hepatic transplantation (Bhat 2009[45], Lee 2010[46], Valdivieso 2010[47]) and were included as exploratory outcomes in H2304. Clinical relevance is justified by the fact that a large proportion of hepatic transplants are due to progression of chronic HCV infection or hepato-cellular carcinoma. Therefore, inclusion of these outcomes in the network meta-analysis could potentially inform questions of clinical interest.

A13. **Priority Question.** The Company submission identified potential treatment modifiers (described in Table 18). Please explain why these covariates were not taken into account with treatment-by-covariate interactions in a meta-regression model to try to reduce the impact of bias.

An attempt was made to use a meta-regression model, but due to the paucity of studies, covariate analyses could not be robustly performed. The treatment effect modifiers were analysed through extensive outcome-specific scenario analyses (section 6.7.7).

A14. **Priority Question.** Please summarise the information provided on pages 87 – 92 in a table. As indicated in Jansen et al 2011, the ERG considers that the key study and patient characteristics of each study included in the NMA should be provided in a Table format. This is essential to judge whether there are differences across trials that might act as effect modifiers, causing bias in the analysis. Furthermore, point estimates and the corresponding measures of uncertainty should be reported for each treatment arm of the individual trials, as well as the relative treatment effects for each of the RCTs included in the NMA.

This allows comparisons between the pooled results of the NMA and the individual study results. Please ensure that data on the number of UK patients in the trial, dose of tacrolimus and the baseline estimated glomerular filtration rate (eGFR) are included as these will be crucial for the generalisability of results?

Please see Section 10.14.2 for a tabular description of the data used in the NMA.

The number of UK patients in trial H2304 was as follows: n = [redacted] (from 2 UK centres). No other trial in the evidence synthesis reported UK specific patient numbers. The requested data on the UK patients are not reported separately in the available CSRs - the UK patients were included in the Europe sub-group for analysis by region. There was a total of 418 patients across all arms in the European region and the baseline mean eGFR was [redacted] ml/min/1.73m^2 [redacted] in the everolimus, tacrolimus elimination, tacrolimus control arms respectively). Average daily tacrolimus dose for the Europe region started at [redacted] mg per day in the TAC control arm (days 3-7) to [redacted] mg per day (week 5) to [redacted] mg a day at month 12. At month 12 the mean daily dose of tacrolimus in the everolimus arm was [redacted] mg.

A15. **Priority Question.** Please explain the rationale behind the selection of the uniform parameters (0 and 5) for the prior distribution selected for the heterogeneity parameters.

Both fixed and random treatment effects models with a common interaction term were fitted. The basic parameters d_{1k} and b are given non-informative normal priors N(0,100^2) (for the treatment effect) and σ ~ Uniform(0,5) (for the between-trial SD). This was based upon the approach taken in the NICE DSU Technical Support Document 2.

A16. **Priority Question.** Please provide further justification as to why the fixed effects model was chosen over the random effects one (beside the DIC scores). NICE DSU guidance (Dias et al, 2014) suggests that the posterior mean of the deviance is presented with the DIC statistics to ensure that the model chosen provides the best fit to the data. Leverage plots would also be useful.

The table below (Table R4) shows the DIC scores and the posterior mean of the deviance. The posterior mean of the deviance suggests that for BPAR free at 3 months, a random effects model fit the data more closely; however the DIC score suggests the opposite. For BPAR free at 6 months, the DIC and posterior mean of the deviance both suggest a random effects model should be selected. An examination of the leverage plots for this analysis (the only plots Novartis could produce during the time period for question response), the analysis shows that both random and fixed effects models have adequate fit. For BPAR free at 12 months, The DIC scores also suggest that a random effects model was chosen, however an analysis of the posterior mean of the deviance suggests a fixed effects model was a better fit to the data. For the renal function comparison, the DIC suggests a fixed effect is the best fit, and the posterior mean of the deviance suggests that the fixed effect model fits the number of data points. The fixed effects models were chosen for use in the *de novo* cost-effectiveness model for the outcomes used in the model.

Table R4: Model fit statistics

Outcome Measure	Fixed Effects			Random Effects			Model presented
	DIC	Dbar	pD	DIC	Dbar	pD	
Overall Survival 12 months	133.3	115.3	17.9	134.8	115.3	19.5	FE
Overall Survival 24 months	83.2	71.4	11.8	85.0	71.8	58.6	FE
Graft survival 12 months	127.8	97.8	15.9	129.6	98.5	16.9	FE
Graft survival 24 months	86.3	74.3	11.9	88.2	75.1	13.1	FE
tBPAR 3 months	138.3	121.4	16.9	139.9	120.9	18.9	FE/RE
tBPAR 6 months	79.9	68.9	11.0	79.5	67.4	12.0	RE/FE
tBPAR 12 months	119.7	105.6	14.1	119.3	102.5	16.9	RE/FE
Renal function (eGFR) 12 months	-0.8	-3.8	3.0	0.3	-4.2	4.4	FE/RE
Withdrawals due to AEs 12 months	68.6	57.7	10.9	68.0	56.7	11.4	RE/FE
Hypertension 12 months	75	65.0	10.1	76.9	65.8	11.1	FE
New onset diabetes 12 months	72.1	62.1	10.0	74.0	62.9	11.0	FE
Infections 12 months	117.0	102.0	15.0	119.1	102.7	16.4	FE
HCV recurrence 12 months	71.5	61.6	10.0	73.1	61.9	11.2	FE

Figure 1: Leverage plot for FE model for tBPAR 6 months

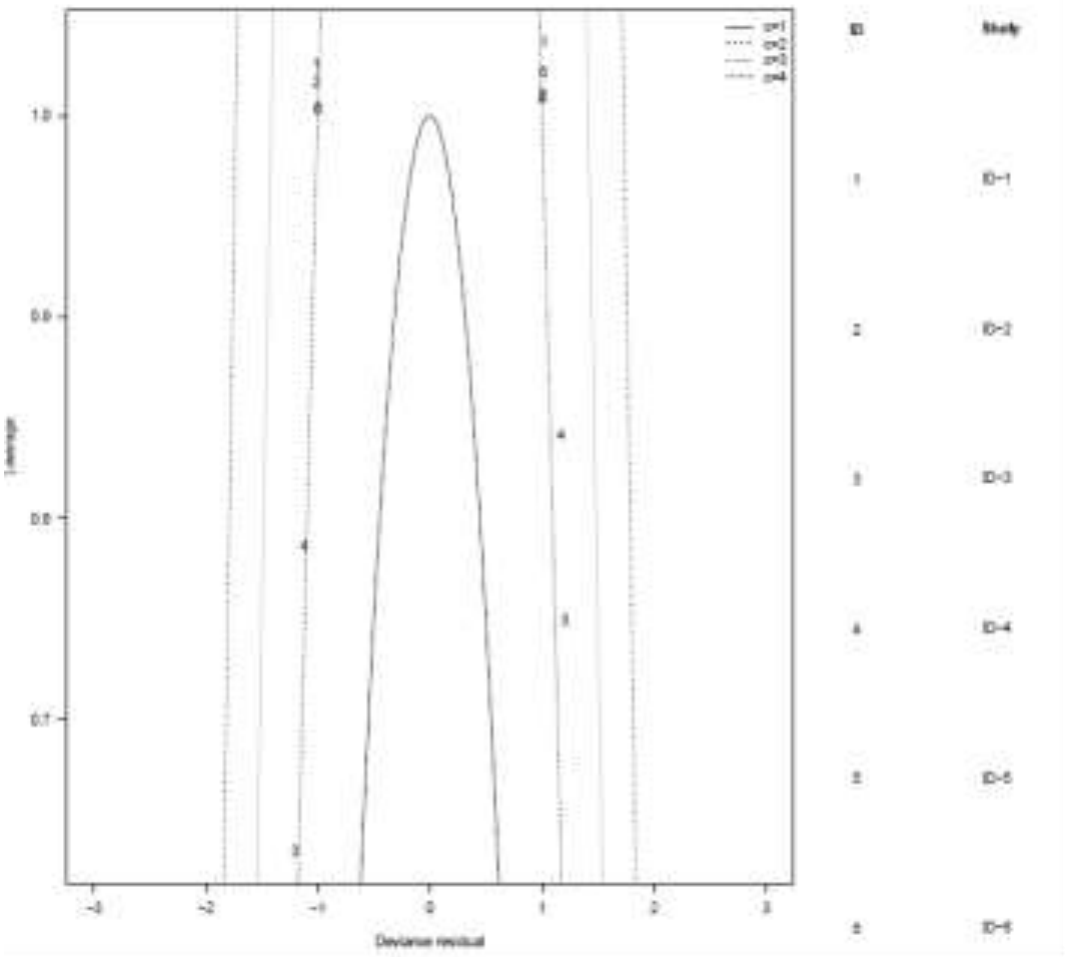
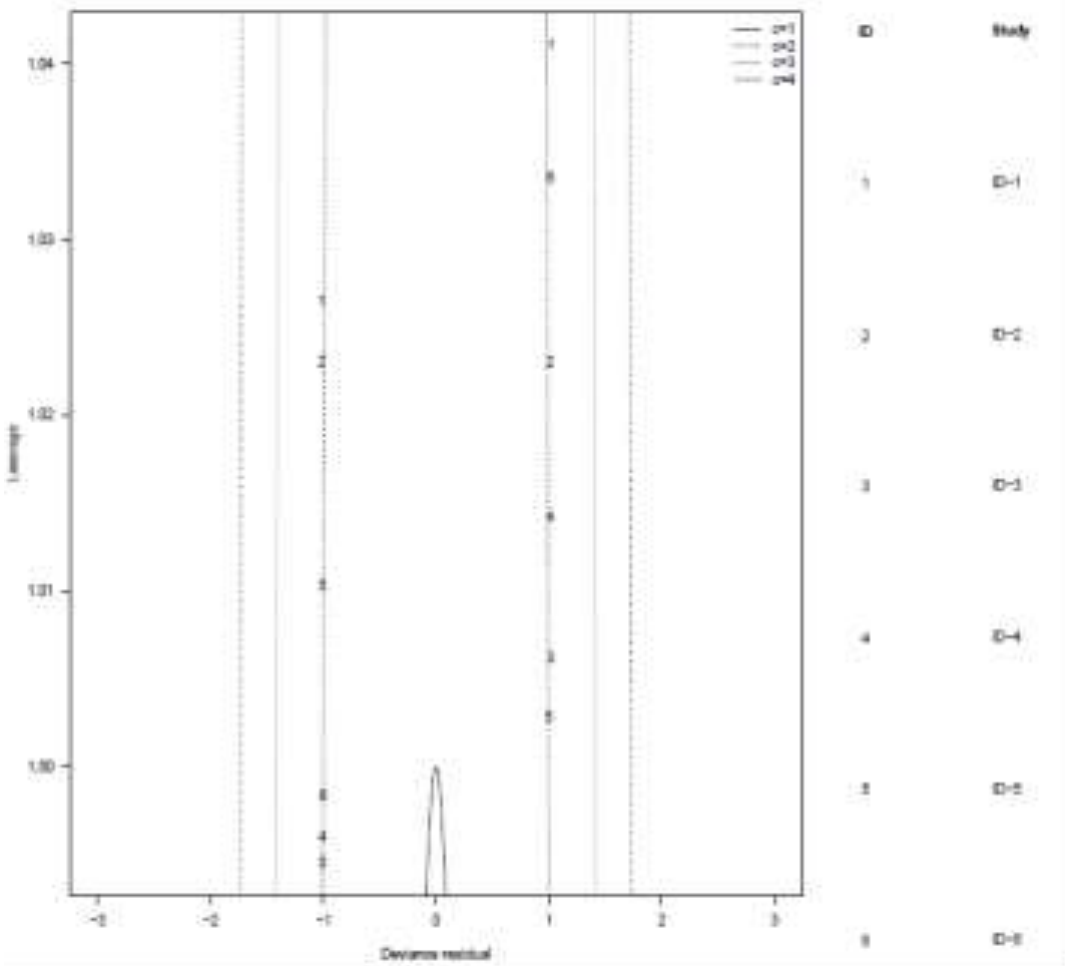


Figure 2: Leverage plot for RE model BPAR 6 months



A17. **Priority Question.** Please provide the following information relating to Tables 23 to 37: 1) present the probability of being the best treatment for each treatment as a ranking of the drugs' effectiveness; 2) explain the similarity of the results for the inconsistency and consistency models - for example, on Table 23 all point estimates (with the exception of one) are exactly the same, with credible intervals (CrI) following the same pattern; 3) provide further interpretation of the results from a clinical and biological point of view on all tables, for example, Table 28 presents CrI between 0 and 267900 for everolimus + reduced tacrolimus compared with azathioprine + standard tacrolimus. What is the clinical relevance of such high values?

1) Table R5 to Table R20 provide the absolute results for the outcomes presented in the NMA (corresponding to tables 23-37), including the ranking and the probability of being the best therapy for the respective outcome.

Time to event results

For Overall Survival and graft loss, the set of studies included in the 12 month analysis was different from the 24 month analysis and the analyses were run separately. Similarly, for time BPAR free, the studies included in the networks varied for 3, 6, and 12 months. Therefore there is a risk of incompatibility between the results for expected absolute values.

When all baseline values for overall survival were used for respectively the 12 month and 24 months analysis, expected absolute point estimates for OS at

12 months were not compatible with those for OS at 24 months, for the MMF + CIC and the EVR + reduced TAC treatments (results not shown). An attempt was made to improve this issue by using only the studies included in both the 12 and 24 months analyses to calculate the weighted mean standard TAC values (i.e. Takada 2013 (Takada *et al.*, 2013[15]), Klintmalm 2007 (Klintmalm *et al.*, 2007[25]), Gonzalez 2005 (Garcia-Gonzalez *et al.*, 2005[2]), Jain 1998 (Jain *et al.*, 1998[26]) and H2304(de Simone *et al.*, 2012[1], Saliba, 2013[27], Saliba *et al.*, 2014[28])). The expected absolute point estimates for OS at 12 and at 24 months were compatible for EVR + reduced TAC (87.1% [95%CrI: 71.1; 94.9] at 12 months and 85.3% [95%CrI: 72.5; 92.9] at 24 months), but the issue remains for MMF + CIC (78.0% [95%CrI: 38.3; 93.6] at 12 months and 88.9% [95%CrI: 43.6; 98.8] at 24 months). The wide credible intervals for MMF + CIC reflect the high uncertainty for this treatment effect and explain why reliable point estimates are not obtained.

When all baseline values were used for graft survival for the 12 month and 24 months analysis, expected absolute point estimates for GS at 12 months were not compatible with those for GS at 24 months, for the MMF + CIC treatments (results not shown). Novartis attempted to improve the issue by using only the studies included in both the 12 and 24 months analyses to calculate the weighted mean standard TAC values (i.e. Klintmalm 2007 (Klintmalm *et al.*, 2007[25]), Gonzalez 2005 (Garcia-Gonzalez *et al.*, 2005[2]), Jain 1998 (Jain *et al.*, 1998[26]) and H2304(de Simone *et al.*, 2012[1], Saliba, 2013[27], Saliba *et al.*, 2014[28])). The expected absolute point estimates for GS at 12 and at 24 months still do not match for MMF + CIC (71.1% [95%CrI: 37.7; 89.0] at 12 months and 86.0% [95%CrI: 49.4; 97.5] at 24 months). The wide credible intervals for MMF + CIC reflect the high uncertainty for this treatment effect and explain why reliable point estimates are not obtained.

For BPAR free, the expected absolute point estimates do not match for the standard TAC, MMF + CIC and MMF + standard TAC treatments. An attempt was made to improve the issue by using only the studies included in the 3, 6 and 12 months analyses to calculate the weighted mean standard TAC values (i.e. Boudjema 2011 and H2304). The expected absolute point estimates for BPAR free were now compatible for standard TAC (81.6% [95%CrI: 76.7; 86.0] at 3 months, 79.2% [95%CrI: 74.1; 83.8] at 6 months and 75.5% [95%CrI: 70.1; 80.3] at 12 months); for MMF + CIC (84.0% [95%CrI: 68.0; 92.8] at 3 months, 78.5% [95%CrI: 0.2; 100] at 6 months and not available at 12 months); for MMF + standard TAC (88.7% [95%CrI: 82.7; 92.9] at 3 months, 84.3% [95%CrI: 1.7; 100] at 6 months and 83.8% [95%CrI: 63.6; 94.6] at 12 months). However, an incompatibility problem appeared for azathioprine plus ciclosporin (79.4% [95%CrI: 62.9; 89.7] at 3 months, 70.6% [95%CrI: 0; 100] at 6 months and 72.7% [95%CrI: 41.8; 91.9] at 12 months). The wide credible intervals for azathioprine plus ciclosporin at 6 and 12 months reflect the high uncertainty for this treatment effect and explain why reliable point estimates are not obtained. The same issue for azathioprine plus ciclosporin was observed with a fixed effects model at all time-points (71.1% [95%CrI: 27.9; 93.4] at 6 months and 72.3% [95%CrI: 55.4; 84.6] at 12 months). Even with a fixed effects model, the credible limits obtained are still considerably wide.

Renal results

The renal results indicate that the therapy which saw the lowest absolute decline in renal function at 12 months was azathioprine plus ciclosporin, followed by EVR + reduced TAC, MMF + reduced TAC and finally, standard TAC. The confidence intervals show some overlap between therapies. However, as ciclosporin has limited use in the UK, and the comparators of interest are used in combination with standard dose tacrolimus, only the absolute value for standard dose tacrolimus was used in the economic model.

Adverse events

There results of the networks for adverse events generally indicate that EVR + reduced TAC had a similar profile to the other treatments. All the credible intervals for the absolute values of each adverse event considered in the NMA have strong overlap. This is reflected in the economic model via probabilistic sensitivity analysis.

2) The inconsistency model results were only presented when a closed loop was present in the network. Details of the inconsistency models were discussed in 6.7.8. If the model is consistent, we would expect the values in the inconsistency model to be similar. For overall survival at 12 months, Table 23, there was a small difference for azathioprine plus ciclosporin versus azathioprine plus standard tacrolimus, but there were no other inconsistencies present between the direct and indirect treatment estimates, hence the similar estimates.

3) Where values present wide credible intervals, the clinical interpretation would be that there is a high level of uncertainty surrounding these estimates, and therefore these should be interpreted with caution.

Table R5: Expected absolute results for overall survival at 12 months (fixed effects model)

Intervention	Absolute estimate 95% CrI Ranking
standard TAC	91.3% 88.5% 93.7% 3
AZA + CIC	76.1% 36.6% 92.6% 7
AZA + standard TAC	92.8% 88.4% 95.8% 2
MMF + CIC	78.0% 38.3% 93.6% 6
MMF + standard TAC	92.0% 88.1% 94.9% 2
MMF + reduced TAC	91.1% 83.6% 95.3% 3
EVR + reduced TAC	87.1% 71.1% 94.9% 5

Table R6. Expected absolute results for overall survival at 24 months (fixed effects model)

Intervention	absolute estimate 95% CrI Ranking
standard TAC	87.4% 84.1% 90.2% 3
AZA + standard TAC	85.8% 76.7% 91.8% 4
MMF + CIC	88.9% 43.6% 98.8% 2
MMF + standard TAC	88.4% 83.8% 92.0% 2
EVR + reduced TAC	85.3% 72.5% 92.9% 4

Table R7. Expected absolute results for graft survival at 12 months (fixed effects model)

Intervention	absolute estimate 95% CrI Ranking
standard TAC	87.9% 84.8% 90.7% 3
AZA + CIC	70.2% 37.5% 88.2% 6
AZA + standard TAC	89.5% 84.2% 93.2% 2
MMF + CIC	71.1% 37.7% 89.0% 6
MMF + standard TAC	90.5% 86.3% 93.7% 2
MMF + reduced TAC	89.2% 79.6% 94.6% 3
EVR + reduced TAC	80.4% 63.4% 90.6% 5

Table R8. Expected absolute results for graft survival at 24 months (fixed effects model)

Intervention	absolute estimate 95% CrI Ranking
standard TAC	82.6% 79.1% 85.8% 3
AZA + standard TAC	80.8% 70.6% 88.2% 4
MMF + CIC	86.0% 49.4% 97.5% 2
MMF + standard TAC	85.3% 80.0% 89.6% 2
EVR + reduced TAC	79.7% 67.3% 88.4% 4

Table R9. Expected absolute results for BPAR at 3 months (fixed effects model)

Intervention	absolute estimate 95% CrI Ranking
standard TAC	81.6% 76.7% 86.0% 6
AZA + CIC	79.4% 62.9% 89.7% 7
AZA + standard TAC	86.2% 80.2% 90.6% 4
MMF + CIC	84.0% 68.0% 92.8% 5
MMF + standard TAC	88.7% 82.7% 92.9% 3
MMF + reduced TAC	90.8% 85.4% 94.5% 2
EVR + reduced TAC	98.1% 93.5% 99.7% 1

Table R10. Expected absolute results for BPAR at 6 months (random effects model)

Intervention	absolute estimate 95% CrI Ranking
standard TAC	79.2% 74.1% 83.8% 4
AZA + CIC	70.6% 0.0% 100.0% 6
AZA + standard TAC	78.5% 0.0% 100.0% 5
MMF + CIC	78.5% 0.2% 100.0% 5
MMF + standard TAC	84.3% 1.7% 100.0% 4
MMF + reduced TAC	83.7% 15.5% 99.3% 4
EVR + reduced TAC	94.2% 11.4% 99.3% 1

Table R11. Expected absolute results for BPAR at 6 months (fixed effects model)

Intervention	absolute estimate 95% CrI Ranking
standard TAC	80.4% 75.8% 84.6% 4
AZA + CIC	71.1% 27.9% 93.4% 7
AZA + standard TAC	78.7% 33.6% 96.0% 5
MMF + CIC	78.7% 37.3% 95.4% 5
MMF + standard TAC	84.6% 56.3% 95.8% 3
MMF + reduced TAC	83.8% 77.9% 88.5% 3
EVR + reduced TAC	94.4% 88.5% 97.9% 1

Table R12. Expected absolute results for BPAR at 12 months (random effects model)

Intervention	absolute estimate 95% CrI Ranking
standard TAC	75.5% 70.1% 80.3% 4
AZA + CIC	72.7% 41.8% 91.9% 5
AZA + standard TAC	74.8% 51.4% 89.3% 5
MMF + standard TAC	83.8% 63.6% 94.6% 2
MMF + reduced TAC	80.5% 57.8% 92.4% 3
EVR + reduced TAC	88.9% 61.7% 97.5% 1

Table R13. Expected absolute results for BPAR at 12 months (fixed effects model)

Intervention	absolute estimate 95% CrI Ranking		
standard TAC	72.0%	76.8% 4	81.2%
AZA + CIC	55.4%	72.3% 6	84.6%
AZA + standard TAC	65.3%	75.6% 5	83.7%
MMF + standard TAC	75.8%	83.4% 2	88.9%
MMF + reduced TAC	74.3%	80.6% 3	85.9%
EVR + reduced TAC	82.3%	89.5% 1	94.4%

Table R14. Expected absolute results for renal function at 12 months (fixed effects model)

Intervention	absolute estimate 95% CrI Ranking		
standard TAC	-32.3	-31.6 4	-30.9
AZA + CIC	-24.2	-14.5 1	-4.9
MMF + reduced TAC	-32.3	-28.2 3	-24.1
EVR + reduced TAC	-27.4	-23.1 2	-18.7

Table R15. Expected absolute results for withdrawals due to adverse events at 12 months (random effects model)

Intervention	absolute estimate 95% CrI Ranking
standard TAC	14.5% 10.2% 19.5% 4
AZA + CIC	0.6% 0.0% 46.3% 1
AZA + standard TAC	8.1% 0.0% 90.5% 4
MMF + standard TAC	4.2% 0.0% 99.7% 3
MMF + reduced TAC	9.1% 0.0% 98.4% 4
EVR + reduced TAC	24.4% 0.1% 99.5% 5

Table R16. Expected absolute results for withdrawals due to adverse events at 12 months (fixed effects model)

Intervention	absolute estimate 95% CrI ranking
standard TAC	14.3% 10.0% 19.2% 4
AZA + CIC	2.3% 0.3% 9.6% 1
AZA + standard TAC	14.6% 6.1% 29.7% 5
MMF + standard TAC	4.2% 0.9% 16.2% 2
MMF + reduced TAC	9.1% 5.2% 15.0% 3
EVR + reduced TAC	24.2% 15.2% 36.0% 6

Table R17. Expected absolute results for hypertension at 12 months (fixed effects model)

Intervention	absolute estimate 95% CrI ranking
standard TAC	37.9% 32.3% 43.7% 3
AZA + CIC	57.8% 28.7% 83.2% 5
MMF + standard TAC	23.9% 14.2% 37.0% 1
MMF + reduced TAC	27.5% 21.0% 35.0% 2
EVR + reduced TAC	40.3% 29.1% 52.4% 4

Table R18. Expected absolute results for new onset diabetes at 12 months (fixed effects model)

Intervention	absolute estimate 95% CrI ranking
standard TAC	13.2% 9.6% 17.1% 2
AZA + standard TAC	18.3% 7.8% 36.1% 4
MMF + standard TAC	19.3% 7.7% 40.6% 4
MMF + reduced TAC	11.6% 7.6% 16.7% 1
EVR + reduced TAC	15.7% 9.7% 24.0% 4

Table R19. Expected absolute results for infections at 12 months (fixed effects model)

Intervention	absolute estimate 95% CrI ranking
standard TAC	59.4% 54.1% 65.0% 4
AZA + CIC	53.5% 30.4% 74.4% 2
AZA + standard TAC	60.3% 45.9% 73.8% 4
MMF + CIC	55.8% 31.0% 77.1% 2
MMF + standard TAC	62.6% 48.8% 74.6% 5
MMF + reduced TAC	62.4% 53.7% 70.5% 5
EVR + reduced TAC	65.7% 56.4% 74.1% 6

Table R20. Expected absolute results for HCV recurrence at 12 months (fixed effects model)

Intervention	absolute estimate 95% CrI ranking
standard TAC	23.5% 19.2% 28.2% 2
AZA + standard TAC	15.1% 8.4% 25.4% 1
MMF + standard TAC	28.6% 20.3% 38.7% 4
MMF + reduced TAC	31.7% 17.3% 50.7% 4
EVR + reduced TAC	31.8% 20.5% 45.7% 4

A18. **Priority Question.** On page 104 the Company submission reports that at 12 months everolimus+reduced tacrolimus is more efficacious than mycophenolate mofetil (MMF) +reduced tacrolimus (Table 32). Please provide a clinical interpretation for these results since the benefit of improved renal function is thought to come from reduced dosages of tacrolimus (which both

everolimus and MMF present in this case). Please also explain from a clinical point of view why in Table 33 everolimus+reduced tacrolimus is comparable (and not more efficacious as in Table 32) than MMF+reduced tacrolimus. Please also explain why everolimus+reduced tacrolimus is so much more effective than standard tacrolimus, In addition, why are MMF+reduced tacrolimus and azathioprine+ciclosporin comparable and more effective than standard tacrolimus respectively, when everolimus+reduced tacrolimus is supposed to be comparable to both MMF+reduced tacrolimus and azathioprine+ciclosporin in terms of relative effectiveness?

Novartis has responded to this priority question by separately addressing the three points in this question.

a) Please provide a clinical interpretation for these results since the benefit of improved renal function is thought to come from reduced dosages of tacrolimus (which both everolimus and MMF present in this case).

It should be noted that trials that inform the reduced tacrolimus + MMF node in the network relevant to these tables define reduced dose tacrolimus as a blood concentration of <8ng/ml. This should be contrasted with the target of 3-5 ng/ml in the everolimus arm of H2304. In both tacrolimus and MMF trials, the mean tacrolimus blood concentration was around 8ng/ml at the end of the follow-up period (approximately 12 months). On this basis, the clinical expectation is, that due to the differing definitions of 'low-dose tacrolimus' the everolimus intervention would be expected to show some benefit with regard to improved renal function as the exposure to tacrolimus is significantly lower.

b) Please also explain from a clinical point of view why in Table 33 everolimus+reduced tacrolimus is comparable (and not more efficacious as in Table 32) than MMF+reduced tacrolimus.

This does not have a clinical interpretation and can be explained by the use of an effect size analysis (to enable the use of two renal function measures) and the transformation of the data (from the results reported for effect size in Table 32) back to change from baseline (CFB) in Table 33.

Renal function is measured using eGFR or eCCr. In order to combine the results of the eGFR and eCCr measures in one analysis, effect size (ES) analyses were conducted. This means that the difference between the least square mean at follow-up (LS mean at FU) or the change from baseline (CFB) for the baseline comparator versus the active treatment was divided by the pooled standard deviation (SD) so that both measurements were standardized and can be combined in one analysis. Effect size analyses allow making consistent theoretical comparison between two different measurement scales that report information for the same outcome. eGFR and eCCr both measure the renal function.

Table 32 compares the difference in effect size of renal function at 12 months, while Table 33 transforms the difference in effect size into the difference in change from baseline. The values used in Table 33, therefore, are obtained by multiplying the effect sizes by the standard deviation for an eGFR measurement. Further information on this change is given below.

The pooled SD is calculated as follows:

$$pooled\ SD = \sqrt{\frac{(N_{active}-1)*SD^2_{active}+(N_{comparator}-1)*SD^2_{comparator}}{N_{active}+N_{comparator}-2}}$$

The associated standard error (SE) of the effect size is calculated using the following formula:

$$SE\ of\ the\ effect\ size = \sqrt{\frac{N_{active}+N_{comparator}}{N_{active}*N_{comparator}}+\frac{ES^2}{2*(N_{active}+N_{comparator})}}$$

If the LS mean at FU or the CFB is reported it will be used to calculate the effect size otherwise it will be calculated based on the difference between the values reported at baseline and at the time-point considered.

If the SD for each treatment is reported it will be used to calculate the pooled standard deviation otherwise it will be calculated based on the following formula:

$SD = SE*\sqrt{1/N}$ or

In the case that the SD or SE is not reported, the SD will be imputed using the following steps:

Step 1. Calculate the SD where the SE is available

Step 2. Calculate the average SD

Step 3. Impute the SD where it is missing by the average SD.

For effect size results, the overall intervention effect is difficult to interpret as it was reported in units of standard deviation rather than in units of any of the measurement scales. In order to transform back the results in terms of differences in eGFR CFB at 1 year for each possible pairwise comparison, the pooled results were multiplied by the typical standard deviation for eGFR measurement.

However, a scenario analysis which included the same three comparisons (everolimus plus reduced tacrolimus, standard tacrolimus, azathioprine plus ciclosporin and MMF plus reduced tacrolimus), but only including the studies that used eGFR as a measure of renal function was found to be insensitive for the results. Please note that within the submission (6.7.7), the text describing this scenario states that “i.e. removing MMF + standard TAC arm from the network.” This statement is an error. There is no MMF plus standard tacrolimus arm for renal function at 12 months analysis.

c) Please also explain why everolimus+reduced tacrolimus is so much more effective than standard tacrolimus, In addition, why are MMF+reduced tacrolimus and azathioprine+ciclosporin comparable and more effective than standard tacrolimus respectively, when everolimus+reduced tacrolimus is supposed to be comparable to both MMF+reduced tacrolimus and azathioprine+ciclosporin in terms of relative effectiveness?

From a clinical perspective, reduction of calcineurin inhibitor dose has been shown to slow the decline of renal function (Geissler 2009, Gonwa 2001). In

the analysis for renal function at 12 months (informed by five studies), azathioprine plus ciclosporin (informed by two small studies) is found to be the most effective of the therapies versus standard tacrolimus in slowing the decline in renal function. This comparison was largely influenced by data from the McDiarmid et al. study. However, some caution should be used when interpreting the relative treatment effect of azathioprine plus ciclosporin for three key reasons relating to this study:

1) The trial is based on small patient numbers and is relatively old (1993);
2) The trial did not report many baseline characteristics and it was difficult to therefore assess the impact of the potential treatment effect modifiers on the results of this analysis;
3) The relative effect of the ciclosporin arm is inconsistent over time.

The figure below indicates that while azathioprine plus ciclosporin has a positive impact on renal function decline in comparison to standard tacrolimus, the relationship is not entirely clear, as at nine months, the effect reverses direction for the ciclosporin arm. This may be due to the small number of patients in this study, or because of other reasons not reported in the study.

Figure 3: eGFR decline in the McDiarmid et al study

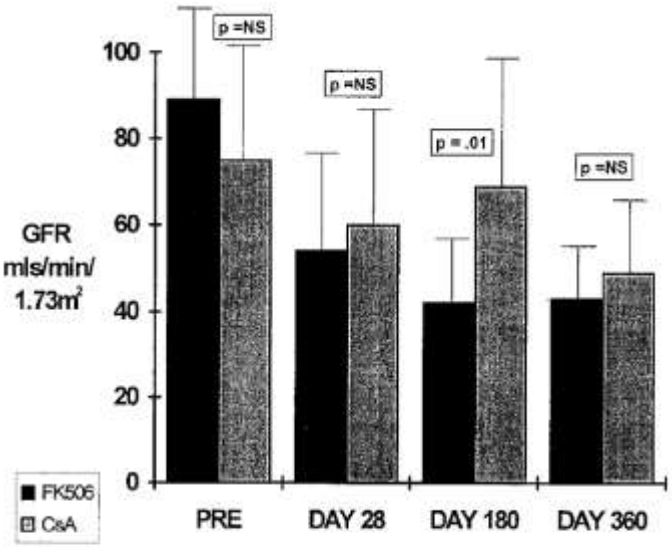


FIGURE 3. A comparison of the mean GFR (with standard deviation) for FK-506-treated patients and CsA-treated patients is shown pretransplant and at days 28, 180, and 360 post-transplant. Only at day 180 was there a weakly significant difference between the two groups.

The result of the indirect treatment comparison for renal function at 12 months was only possible by conducting the standardised effect to include both measures of renal function. This combined with the two small studies informing the effect size for azathioprine plus ciclosporin introduces some uncertainty surrounding the results of the analysis. However, the H2304 study demonstrates key evidence for the relative effectiveness of everolimus plus reduced tacrolimus in comparison to tacrolimus and this can be explained from a clinical perspective because of the renal toxicity associated with CNI use. This is well documented and a key issue in liver transplantation (Geissler *et al.*, 2009[29]) (Gonwa *et al.*, 2004[30]). A 2003 UNOS study found that 20% of

liver transplant patients were in a state of chronic renal failure 5 years after transplant (Ojo *et al.*, 2003[31]). Furthermore the studies included in the evidence base for de novo MMF and 'reduced' dose tacrolimus showed no difference in renal function at month 12 between the 'reduced' dose and 'standard' dose tacrolimus arms (Goralczyk *et al.*, 2012[32]). Therefore it is entirely clinically plausible that the intervention of everolimus and a significantly lower dose of tacrolimus at an early stage post-transplant would be more effective than standard tacrolimus with regard to preservation of renal function. Following discussion with the clinical experts it was considered to focus on tacrolimus because combinations of tacrolimus (with azathioprine/MMF) were only relevant to use in the clinical practice in the UK. This explains our rationale for the focus on using the data (tacrolimus only data from the indirect treatment comparison) for these specific comparisons in the economic model.

A19. On page 63 it is mentioned that "*baseline characteristics appear similar in all treatment arms"* however, Table 8 on page 56 shows that a higher percentage of HCV patients in the everolimus arm of the trial and a higher percentage of hepatocellular carcinoma cases in the tacrolimus arm. Please explain these imbalances.

Apologies - the figures for HCV and HCC have been transposed in error in table 8. These figures have been checked with the CSR and for the tacrolimus control arm the numbers are 31.3% and 14.4% for HCV positive and HCC respectively. As stated on page 63, these are similar to the relevant numbers in the everolimus arm (31.8% and 17.1% respectively).

Section B: Clarification on cost-effectiveness data

B1. **Priority Question.** The ERG is not convinced that 3 month cycles can capture all the relevant outcomes for the disease modelled. For example, on page 153 the Company submission states that *"Three days of high dose steroids are used to treat detected acute rejection (for example, 1000mg of methylprednisolone) with around 85 to 90 percent success rates of therapy. If this therapy fails, it is repeated again 3 days later with the same success rate."* This suggests people should be able to progress through the states in the model much faster than is currently allowed. Please clarify whether all the clinical outcomes which take place in shorter periods of times are captured in the model, and if so, please demonstrate this.

The three month cycle length was validated with clinical experts who advised that the timing of any acute rejection was likely to occur within the three month period, but that the majority of patients would move back to the stable state after treatment. Clinical experts also verified that 'acute rejection' and 'acute steroid resistant rejection' were mostly symptomless stages, where no additional healthcare costs would be incurred or benefits be gained. Whilst the model does assume the movement to and from this state would last a three month cycle, we would not expect that shortening the cycle length to necessarily have an impact on the results of the model, as the costs of the acute rejection state are the same as the stable post-transplant state (with the exception of the relatively small cost of high dose corticosteroids) and the utility is also the same (0.58). As 98.1% of patients in all treatment arms return

to a stable state after treatment for acute rejection, changing this cycle to less than 3 months would have virtually no impact on the model outcomes.
The clinical experts also confirmed that patients would be unlikely to experience mild chronic rejection or graft loss within the initial 3 months post-transplant. These assumptions were also based upon a study by Aydogan et al, (Aydogan *et al.*, 2010[33]) which found that the vast majority of patients move in and out of acute rejection, but are mostly successfully treated with high dose corticosteroids.

B2. **Priority Question.** On page 142, Table 46, please clarify the renal related death estimation process. The probability of death in this state should be related with renal functioning.

Table 46 contains a typo, apologies for this. In the 'death' state, the definition should read "Patients have increased mortality risk in CKD 5 and this is captured in the renal-related death state in the model. Natural (background) mortality risk is applied at all stages of the model."

As this model is made up of a hepatic model and a renal model, the probability of death is calculated independently for each model. The model then 'checks' to see if patients have died in either model before returning a dead health state for both models. In the hepatic model, the probability of death is dependent on the previous health state and the time since transplant. This model assumes that with the exception of the graft loss health state, death is dependent on natural mortality, which is based upon the life tables for England and Wales. Transition probabilities for the hepatic model are presented below (Table R21). The probability of being in any health state, including death is compared to a random number. If the probability of being in that health state is greater than the random number, a patient is said to be in that health state.

The renal sub-model uses the same approach as the hepatic model. Death is determined by both the previous state and the probability of moving from a particular state to death. However, if a patient has died from background mortality or hepatic-related mortality, the patient is also considered dead in the renal model. The transition probabilities for the renal model are presented in Table R22.

Table R21: Transition probabilities in the hepatic model

From health state	To health state	p(EVER)	p(AZA)	p(MMF)	Assumption	Reference / source
First 3 months in state						
Stable post-transplant state	Stable post-transplant state	98.1%	86.2%	88.7%	1 - P(leaving state)	Calculation
	Acute rejection	1.9%	13.8%	11.3%	Probability constant over this 3 month period	Data from the NMA
	Mild chronic rejection	0.0%	0.0%	0.0%	Only after 12 months in state this can occur	*Assumption*
	Liver-related death	0.0%	0.0%	0.0%	Natural mortality only	(ONS, 2012[34])
Acute rejection	Stable post-transplant state	98.1%	98.1%	98.1%	Multiple courses of steroid therapy to stop AR	(Aydogan *et al.*, 2010[33])
	Acute steroid resistant rejection	1.9%	1.9%	1.9%	1 - P(leaving state)	Calculation
	Mild chronic rejection	0.0%	0.0%	0.0%	Only after 12 months in state this can occur	*Assumption*
	Liver-related death	0.0%	0.0%	0.0%	Natural mortality only	(ONS, 2012[34])
Acute steroid resistant rejection	Stable post-transplant state	83.3%	83.3%	83.3%	Antilymphocyte therapy	(Aydogan *et al.*, 2010[33])
	Acute steroid resistant rejection	0.0%	0.0%	0.0%	1 - P(leaving state)	Calculation
	Mild chronic rejection	0.0%	0.0%	0.0%	Only after 12 months in state this can occur	*Assumption*
	Graft loss (severe chronic rejection)	16.7%	16.7%	16.7%	Progression to chronic severe rejection if steroid therapy failed	(Aydogan *et al.*, 2010[33])
	Liver-related death	0.0%	0.0%	0.0%	Natural mortality only	(ONS, 2012[34])
Mild chronic rejection	Stable post-transplant state	0.0%	0.0%	0.0%	Chronic rejection naturally stops and patients become stable	*Assumption*
	Mild chronic rejection	100.0%	100.0%	100.0%	Patients persist in this state unless they die	*Assumption*

	Liver-related death	0.0%	0.0%	0.0%	Natural mortality only	(ONS, 2012[34])
Graft loss (severe chronic rejection)	Stable post-transplant state (via re-transplant)	0.0%	0.0%	0.0%	Patients transplanted between 4 - 6 mths on waiting list	(Organ Donation, 2014[35])
	Graft loss (severe chronic rejection)	97.0%	97.0%	97.0%	1 - P(leaving state)	Calculation
	Death	3.0%	3.0%	3.0%	12% patients die per year on the waiting list, plus natural mortality	(Organ Donation, 2014[35])
From months 4 to 6 in state						
Stable post-transplant state	Stable post-transplant state	96.3%	92.5%	95.9%	1 - P(stable to AR) - P(stable to death)	Calculation
	Acute rejection	3.7%	7.5%	4.1%	Probability constant over this 3 month period	Data from the NMA
	Mild chronic rejection	0.0%	0.0%	0.0%	Only after 12 months in state this can occur	*Assumption*
	Liver-related death	0.0%	0.0%	0.0%	Natural mortality only	(ONS, 2012[34])
Acute rejection	*Not in this state past 3 months*	0.0%	0.0%	0.0%	Not in this state past 3 months	*Assumption*
Acute steroid resistant rejection	Stable post-transplant state	0.0%	0.0%	0.0%	Antilymphocyte therapy failed	*Assumption*
	Acute steroid resistant rejection	83.3%	83.3%	83.3%	1 - P(leaving state)	Calculation
	Mild chronic rejection	0.0%	0.0%	0.0%	Only after 12 months in state this can occur	*Assumption*
	Graft loss (severe chronic rejection)	16.7%	16.7%	16.7%	Progression to chronic severe rejection if steroid therapy failed	(Aydogan *et al.*, 2010[33])
	Liver-related death	0.0%	0.0%	0.0%	Natural mortality only	(ONS, 2012[34])
Mild chronic rejection	Stable post-transplant state	0.0%	0.0%	0.0%	Chronic rejection naturally stops and patients become stable	*Assumption*

	Mild chronic rejection	100.0%	100.0%	100.0%	Patients persist in this state unless they die	*Assumption*
	Liver-related death	0.0%	0.0%	0.0%	Natural mortality only	(ONS, 2012[34])
Graft loss (severe chronic rejection)	Stable post-transplant state (via re-transplant)	99.3%	99.3%	99.3%	Patients transplanted between 4 - 6 mths on waiting list	(Organ Donation, 2014[35])
	Graft loss (severe chronic rejection)	0.0%	0.0%	0.0%	1 - P(leaving state)	Calculation
	Death	0.7%	0.7%	0.7%	Operative death rate	(Aylin *et al.*, 2013[36])
From months 7 to 9 in state						
Stable post-transplant state	Stable post-transplant state	97.6%	98.5%	99.4%	1 - P(leaving state)	Calculation
	Acute rejection	2.5%	1.6%	0.6%	Probability constant over this 3 month period	Data from the NMA
	Mild chronic rejection	0.0%	0.0%	0.0%	Only after 12 months in state this can occur	*Assumption*
	Liver-related death	0.0%	0.0%	0.0%	Natural mortality only	(ONS, 2012[34])
Acute rejection	*Not in this state past 3 months*	0.0%	0.0%	0.0%	Not in this state past 3 months	*Assumption*
Acute steroid resistant rejection	Stable post-transplant state	0.0%	0.0%	0.0%	Antilymphocyte therapy failed	*Assumption*
	Acute steroid resistant rejection	83.3%	83.3%	83.3%	1 - P(leaving state)	Calculation
	Mild chronic rejection	0.0%	0.0%	0.0%	Only after 12 months in state this can occur	*Assumption*
	Graft loss (severe chronic rejection)	16.7%	16.7%	16.7%	Progression to chronic severe rejection if steroid therapy failed	(Aydogan *et al.*, 2010[33])
	Liver-related death	0.0%	0.0%	0.0%	Natural mortality only	(ONS, 2012[34])
Mild chronic	Stable post-	0.0%	0.0%	0.0%	Chronic rejection naturally stops	*Assumption*

rejection	transplant state				and patients become stable	
	Mild chronic rejection	100.0%	100.0%	100.0%	Patients persist in this state unless they die	*Assumption*
	Liver-related death	0.0%	0.0%	0.0%	Natural mortality only	(ONS, 2012[34])
Graft loss (severe chronic rejection)	*Not in this state past 6 months*	0.0%	0.0%	0.0%	Not in this state past 6 months	*Assumption*
From months 10 to 12 in state						
Stable post-transplant state	Stable post-transplant state	97.6%	98.5%	99.4%	1 - P(leaving state)	Calculation
	Acute rejection	2.5%	1.6%	0.6%	Probability constant over this 3 month period	Data from the NMA
	Mild chronic rejection	0.0%	0.0%	0.0%	Only after 12 months in state this can occur	*Assumption*
	Liver-related death	0.0%	0.0%	0.0%	Natural mortality only	(ONS, 2012[34])
Acute rejection	*Not in this state past 3 months*	0.0%	0.0%	0.0%	Not in this state past 3 months	*Assumption*
Acute steroid resistant rejection	Stable post-transplant state	0.0%	0.0%	0.0%	Antilymphocyte therapy failed	*Assumption*
	Acute steroid resistant rejection	83.3%	83.3%	83.3%	1 - P(leaving state)	Calculation
	Mild chronic rejection	0.0%	0.0%	0.0%	Only after 12 months in state this can occur	*Assumption*
	Graft loss (severe chronic rejection)	16.7%	16.7%	16.7%	Progression to chronic severe rejection if steroid therapy failed	(Aydogan *et al.*, 2010[33])
	Liver-related death	0.0%	0.0%	0.0%	Natural mortality only	(ONS, 2012[34])
Mild chronic rejection	Stable post-transplant state	0.0%	0.0%	0.0%	Chronic rejection naturally stops and patients become stable	*Assumption*
	Mild chronic rejection	100.0%	100.0%	100.0%	Patients persist in this state unless they die	*Assumption*

	Liver-related death	0.0%	0.0%	0.0%	Natural mortality only	(ONS, 2012[34])
Graft loss (severe chronic rejection)	*Not in this state past 6 months*	0.0%	0.0%	0.0%	Not in this state past 6 months	*Assumption*
From month 13 onwards						
Stable post-transplant state	Stable post-transplant state	96.6%	97.5%	98.4%	1 - P(leaving state)	Calculation
	Acute rejection	2.5%	1.6%	0.6%	Probability constant over this 3 month period	Data from the NMA
	Mild chronic rejection	1.0%	1.0%	1.0%	After 12 months post-transplant this can occur	*Assumption*
	Liver-related death	0.0%	0.0%	0.0%	Natural mortality only	(ONS, 2012[34])
Acute rejection	*Not in this state past 3 months*	0.0%	0.0%	0.0%	Not in this state past 3 months	*Assumption*
Acute steroid resistant rejection	Stable post-transplant state	0.0%	0.0%	0.0%	Antilymphocyte therapy failed	*Assumption*
	Acute steroid resistant rejection	83.3%	83.3%	83.3%	1 - P(leaving state)	Calculation
	Mild chronic rejection	0.0%	0.0%	0.0%	After 12 months post-transplant this can occur	*Assumption*
	Graft loss (severe chronic rejection)	16.7%	16.7%	16.7%	Progression to chronic severe rejection if steroid therapy failed	(Aydogan *et al.*, 2010[33])
	Liver-related death	0.0%	0.0%	0.0%	Natural mortality only	(ONS, 2012[34])
Mild chronic rejection	Stable post-transplant state	0.0%	0.0%	0.0%	Chronic rejection naturally stops and patients become stable	*Assumption*
	Mild chronic rejection	100.0%	100.0%	100.0%	Patients persist in this state unless they die	*Assumption*
	Liver-related death	0.0%	0.0%	0.0%	Natural mortality only	(ONS, 2012[34])
Graft loss (severe	*Not in this state past 6 months*	0.0%	0.0%	0.0%	Not in this state past 6 months	*Assumption*

chronic rejection)

Table R22: Transition probabilities for the renal model

From health state	To health state	p(EVER)	p(AZA)	p(MMF)	Assumption	Reference / source
No CKD	No CKD	98.3%	98.3%	98.3%	1 - P(leaving state)	Calculation
	CKD stages 1 to 2	1.8%	1.8%	1.8%	Annual probability of progression divided by 4	(La Mattina *et al.*, 2011[37])'Chronic Kidney Disease Stage Progression in Liver Transplant Recipients'
	Death	0.0%	0.0%	0.0%	Natural mortality is assumed	(ONS, 2012[34])
CKD stages 1 to 2	CKD stages 1 to 2	90.8%	90.8%	90.8%	1 - P(leaving state)	Calculation
	CKD stage 3	8.5%	8.5%	8.5%	Annual probability of progression divided by 4	(La Mattina *et al.*, 2011[37])'Chronic Kidney Disease Stage Progression in Liver Transplant Recipients'
	Death	0.7%	0.7%	0.7%	Added mortality risk assumed in CKD stage 2	(Keith *et al.*, 2004[38])
CKD stage 3	CKD stage 3	84.8%	84.8%	84.8%	1 - P(leaving state)	Calculation
	CKD stage 4	14.0%	14.0%	14.0%	Annual probability of progression divided by 4	(La Mattina *et al.*, 2011[37])'Chronic Kidney Disease Stage Progression in Liver Transplant Recipients'
	Death	1.2%	1.2%	1.2%	Added mortality risk assumed in CKD stage 3	(Keith *et al.*, 2004[38])
CKD stage 4	CKD stage 4	97.0%	97.0%	97.0%	1 - P(leaving state)	Calculation
	CKD stage 5	0.8%	0.8%	0.8%	Annual probability of progression divided by 4	(La Mattina *et al.*, 2011[37])'Chronic Kidney Disease Stage Progression in Liver Transplant Recipients'

	Death	2.3%	2.3%	2.3%	Added mortality risk assumed in CKD stage 4	(Keith *et al.*, 2004[38])
CKD stage 5	CKD stage 5	95.4%	95.4%	95.4%	1 - P(leaving state)	Calculation
	Death	4.6%	4.6%	4.6%	Added mortality risk assumed in CKD stage 5	(Keith *et al.*, 2004[38])
CKD stage 5 *(in cycle 14 only)*	CKD stage 5 *(in cycle 14 only)*	0.0%	0.0%	0.0%	1 - P(leaving state)	Calculation
	No CKD via renal transplant *(in cycle 14 only)*	99.3%	99.3%	99.3%	Patients transplanted between 32 - 35 mths on waiting list	(Organ Donation, 2014[39]) (b)
	Death *(in cycle 14 only)*	0.7%	0.7%	0.7%	Operative death rate	(Aylin *et al.*, 2013[36])
Post-renal transplant ("No CKD [T]")	No CKD (T)	98.3%	98.3%	98.3%	Move back into start of model	*Assumption*
	CKD stages 1 to 2	1.8%	1.8%	1.8%	Same progression chance as before transplant	*Assumption*
	Death	0.0%	0.0%	0.0%	Natural mortality is assumed and is already accounted for in the hepatic model	(ONS, 2012[34])

B3. **Priority Question.** For Table 55, on page 159 please clarify how the tacrolimus dosages used in each treatment regimen compare with the UK standard practice (in terms of tacrolimus dosage).

Tacrolimus dosing in liver transplantation should be between 0.10 - 0.20mg/kg according to the SPC. Blood concentrations should be in the range of 5 - 15ng/ml following initiation of therapy. Therefore, given tacrolimus dosing has tended to the lower end of the above ranges in recent clinical practice, it can reasonably be assumed that the dosages stated in the table are generally reflective of UK clinical practice.

B4. **Priority Question.** It is important for the ERG to understand why the ICERs in the company submission are so high. Please include some rationale for this and (if deemed relevant) compare the ICERs in this submission with ones previously presented in the appraisal process for any of the comparator drugs.

It is not possible to compare the ICERs in this submission to any previously presented as no immunosuppressive interventions for liver transplantation have been appraised by NICE, SMC or AWMSG. Indeed, as noted in the cost-effectiveness section, no previous cost-effectiveness analyses considering competing immunosuppressive regimens have been published, necessitating the fully *de novo* approach taken by this submission. It should be noted that all comparators have similarly high efficacy with regard to prevention of rejection-related events. Everolimus is a branded product being compared to generic comparators, which may partially explain the high ICERs presented.

B5. **Priority Question.** Please provide the calculations used to derive the parameters in Tables 53 and 54 for all treatment arms, with regards to taking the NMA odds ratios (ORs) presented in Tables 23 to 37 (section 6) and estimating the probabilities used in the model. Please also explain the rationale behind the sources selected for the model parameters presented in these tables.

The model utilised the absolute value parameters as estimated by the NMA for the following outcomes:

- BPAR free at 3, 6, and 12 months (Table R9 to Table R13)
- eGFR decrease at 12 months (Table R14)
- Hypertension (Table R17)
- New onset diabetes (Table R18)
- Infection (Table R19)

In the absence of head-to-head trial results between comparators, data from the evidence synthesis was used to population the health economic model. For the additional adverse events considered in the model, evidence from the systematic review of the literature was used as this provided the only treatment specific evidence for these parameters. Please see question A18 for a discussion of the calculations which were necessary to obtain estimates of eGFR decrease at 12 months, a key variable for the renal sub-model.

B6. **Priority Question.** On page 149 the Company submission states that *"The expected decrease (as displayed in Table 53) was then applied to the patient in the first year post transplant and their eGFR level after 12 months was then calculated and a patient was assigned to the appropriate CKD [chronic kidney*

disease] state as per the model schematic (section 7.2.2)." Please confirm that the expected decrease in eGFR for each treatment arm is the same irrespective of the eGFR starting value. Please provide the calculations undertaken to estimate the absolute eGFR decrease and the respective relative effectiveness of the drugs between treatment arms presented in Table 53.

Yes, the expected eGFR decrease applied to patients after year one is the same regardless of starting eGFR.

The absolute values as calculated from the NMA were used and the results are presented in Table R14 in the previous question response. The value for standard tacrolimus was used for azathioprine plus standard dose tacrolimus plus corticosteroids and MMF plus standard dose tacrolimus plus corticosteroids. The NMA did not provide evidence for the combination of standard dose tacrolimus with MMF or azathioprine and therefore the value for standard tacrolimus was used within the model (see question A18 for further description of this indirect treatment comparison).

B7. **Priority Question.** Please clarify if any searches were undertaken on utility data used for the renal sub-model. If not, please provide the rationale for this and for selection of the values presented. Also for Table 58, for the disutility data sources, please provide the same details as for the utility data (Table 57). Some disutility values were based on assumptions. Was there any clinical input informing these assumptions? Were any searches done for disutility data?

A pragmatic literature search was conducted for utility values associated with the renal sub-model. The studies used are presented as per Table 57 below.

Table R23: Utility studies used in the renal model

Study, Country	Population	Recruitment Info	No. of Respondents	Assessment Tools	Response Rate %	Health States and Time Period	Utility Values	SD and CIs (for mean values), IQR (for median values)	Appropriateness for CEA
(Neri *et al.*, 2012[40])UK and USA	• Mainly male (61.8%) • Average months since transplant: 63.7	• All patients registered in the renal departmental database of the Cardiff and Vale NHS Trust in September 2002	CKD stage 1-2: 24 CKD stage 3: 65 CKD stage 4: 37 CKD stage 5: 17	EQ-5D	NR	CKD Stage 1-2	0.64 adjusted mean	NR	• UK population
						CKD Stage 3	0.58 adjusted mean	NR	
						CKD Stage 4	0.49 adjusted mean	NR	
						CKD Stage 5	0.28 adjusted mean	NR	
(Liem *et al.*, 2008[41])UK	• Predominately mail (53 – 65%)	Not reported by study	808	EQ-5D	NR	Post renal transplant	0.81 mean	0.72-0.90 (95% CI)	• Data for post-transplant using EQ-5D, not UK specific

Abbreviations: **NR: not reported; CKD: chronic kidney disease**

B8. **Priority Question.** On page 180 the Company submission states that ***"the baseline time point was immediately (one day) post-transplant***. *These patients entered in the model state Stable Post-Transplant. Thus, the baseline HRQL score was equalled to the score in the first cycle. However, disutility was applied upon entry if the patient experienced an adverse event upon entering the mode*l". However throughout the submission it is mentioned that baseline period was considered 30 days post-transplantation. Please clarify this.

The model cycle starts immediately (one day) post-transplant, as the use of comparator therapies begins at this time point. Costs and benefits for everolimus plus reduced tacrolimus plus corticosteroids were adjusted to reflect the later starting point of 30 days post-transplantation, accounting for 2 of the 3 months in the first cycle.

B9. **Priority Question.** Please provide more detail on how the 'utility values adjusted for informative dropout' (Table 60) were obtained.

To provide a fuller account of changes in HRQL post transplantation (by not just focusing on patients who remained alive for the entire follow-up period), an adjustment was made to the data set to allow for informative dropout. Specifically, patients who died at any time post transplantation were given values of 0 (corresponding to the value for death) for the EQ-5D tariff for all subsequent times.

B10. Please confirm whether the resources presented in Table 63 represent the resource use per 3-month cycle.

Yes, the resource use is presented by 3-month cycle.

B11. **Priority Question.** Table 64 is based on a patient average body weight of 73.9kg. Please provide the rationale for choosing this value and explain why some of the unit costs were taken from sources other than BNF.

The average body weight was taken from the H2304 trial and is broadly in keeping with the other studies included in the NMA (Table R24).

The unit costs in the commercial medicines unit are the most recent unit costs available, while BNF 67 has gaps between updates. However, the costs listed in the submission using the commercial medicines unit costs are no different to those in the BNF.

Table R24: Body weight reported in the NMA studies

Number	Name	Year	Weight
1	(de Simone *et al.*, 2012[1])	2012	BMI
2	(Garcia-Gonzalez *et al.*, 2005[2])	2005	Dual therapy - 71.5 Triple therapy - 75
3	(Neuberger *et al.*, 2007[3])	2007	NR
4	(Klintmalm *et al.*, 2011[4])	2011	Arm 1 - 82.3 Arm 2 - 86.8 Arm 3 - 86.0
5	(Boillot *et al.*, 2001[5])	2001	3 month cohort, dual therapy - 69.3 triple therapy - 72.8. 12 month cohort, dual therapy 68.3 triple therapy - 71.5
6	(Fisher *et al.*, 1998[6])	1998	NR
7	(Jain *et al.*, 2002[7])	2002	NR
8	(Junge *et al.*, 2005[8])	2005	NR
9	(Wiesner *et al.*, 2001[9])	2001	MMF - 80.7 AZA - 77.9
10	(Nashan *et al.*, 2009[10])	2009	Standard - 81.8 Reduced 79.0
11	(Greig *et al.*, 2003[11])	2003	NR
12	(Marin Gomez *et al.*, 2011[12])	2011	NR
13	(Neuhaus *et al.*, 1997[13])	1997	NR
14	(Boudjema *et al.*, 2011[14])	2011	Active control - 71 Experimental - 75 All patients - 73
15	(Takada *et al.*, 2013[15])	2013	NR
16	(Dmitrewski *et al.*, 1994[16])	1994	
17	(Porayko *et al.*, 1994[17])	1994	NR
18	(Therapondos *et al.*, 2002[18])	2002	Cyclosporin - 68 Tacrolimus - 74.1
19	(Salizzoni *et al.*, 2001[19])	2001	NR
20	(Manousou *et al.*, 2009[20])	2009	NR
21	Samonakis et al (Samonakis *et al.*, 2006[21])	2006	NR
22	(McDiarmid *et al.*, 1993[22])	1993	NR

B12. **Priority Question.** Please provide the calculations used to derive the parameters in Table 67. More specifically, please explain how the survival probabilities were obtained and why survival and hepatic graft survival include 24 month probabilities?

Where possible, 95% CI (or CrI) were derived from the literature or the network meta-analysis. Where this was not possible, a high and low value was estimated assuming a difference of +/-20% was used. The overall survival estimates listed in Table 67 were derived from the NMA, however, these values are not used in the model and these values should not have appeared in the submission. Novartis apologises for the oversight.

B13. In table 65, the cost of testing eGFR (estimated glomerular filtration rate) has been referenced as the cost for EGFR-TK mutation testing, which is a test undertaken for people with non-small-cell lung cancer. Please provide the correct reference for this cost and provide an updated cost if this is incorrect.

Novartis found no data in the systematic literature review with which to populate this parameter. A pragmatic review was undertaken and at the time of the search (June 2014) no specific cost data was found for eGFR testing within an NHS setting. However, the updated clinical guidelines released in July 2014 recommend the use of eGFRcystatinC and serum creatinine testing to confirm or rule out CKD. The cost of this test is approximately £2.75 (National Institute for Health and Care Excellence, 2014[42]), significantly lower than the previous estimate. The inclusion of the revised cost parameter in the model had a limited impact on the deterministic ICER as the relative impact of this parameter is very small (within the expected change of the ICER between runs of ~£2,000 per QALY gained) given that all patients in all arms would receive an eGFR test, though there may be some differences in the timing of the testing between arms.

Section C: Textual clarifications and additional points

C1. **Priority Question.** Please clarify how the MEDLINE C/E searches have been combined. Page 271 of the submission, line 40, refers to the action 'or/40-43' but there are no lines 42 or 43. Please confirm that line 40 should read '4 AND 7 AND 39' and that line 41 should be a date limit (1990-Current)?

This is a copy and paste error. As stated above, the searches should read '4 AND 7 AND 39' and line 41 date limit (1990-current).

C2. **Priority Question.** In the effectiveness searches (page 252) please confirm that line 10 of the MEDLINE search (line 11 of the EMBASE search, line 10 of the CENTRAL/CDSR search, and Line 3 of the DARE search) is correctly presented. Is the ERG correct in its interpretation that the line should read: (cellcept or mycophenolic acid or morpholinoethyl ester…)? Otherwise the concern is that mycophenolic acid is not being searched as a free-text term and this might impact on the identification of studies.

The search was re-run using the 'or' between mycophenolic acid and morpholinethyl ester. This addendum saw an additional 7 hits included (See Table R25). All abstracts were double reviewed and excluded using the inclusion and exclusion criteria. Therefore, Novartis believes the original search strings were robust. Record details can be found in the table below, as well as the updated search strings.

Table R25: Additional studies identified in the modified search

No..	Authors	Year	Title
1	A. M. Tomillero, M. A.	2010	Summary
2	A. S. C. F. Decavele, N.;Heyden, F. V.;Verstraete, A. G.	2011	Performance of the Roche Total Mycophenolic Acid assay on the Cobas Integra 400, Cobas 6000 and comparison to LC-MS/MS in liver transplant patients
3	C. B. D. Ramirez, C.;Frank, A. M.;Armenti, S	2013	Completely steroid-free immunosuppression in liver transplantation: a randomized study
4	M. Farkkila	2013	[Autoimmune hepatitis]. [Finish]
5	M. R. Bayes, X.;Prous, J	2005	Gateways to clinical trials: October 2005
6	O. A. Eyal, M.;Safadi, R.;Elhalel, M. D.	2013	Serum vitamin D levels in kidney transplant recipients: the importance of an immunosuppression regimen and sun exposure

7	Owers Daniel, S.;Webster Angela, C.;Strippoli Giovanni, F. M.;Kable, Kathy;Hodson Elisabeth, M.	2013	Pre-emptive treatment for cytomegalovirus viraemia to prevent cytomegalovirus disease in solid organ transplant recipients

Table R26: Medline search string comparison including 'or' and the 'mycophenolate sodium' term

Medline Search String	
1	liver transplantation/ (44871)
2	(liver$ adj3 (transplant$ or graft$)).ti,ab. (48183)
3	(hepatic adj3 (transplant$ or graft$)).ti,ab. (2781)
4	1 or 2 or 3 (58416)
5	everolimus.mp. (3444)
6	(everolimus or RAD-001 or "RAD 001" or RAD001 or certican or zortress or afinitor or votubia).mp. (3563)
7	Azathioprine/ (13489)
8	(azathioprin$ or azothioprin$ or aprin or azap or azasan or azimune or azoprine or azoran or immuzat or imuran or immuran or imurel or thiazprine or transimmune or zinothin or zymurine).mp. (20299)
9	mycophenolic Acid/ (6382)
10	(cellcept or mycophenolic acid morpholinoethyl ester or RS 61443 or RS-61443 or mycophenolate mofetil or Mycophenolate mofetil hydrochloride or MMF).mp. (9371)
11	(cellcept or mycophenolic acid or morpholinoethyl ester or RS 61443 or RS-61443 or mycophenolate mofetil or Mycophenolate mofetil hydrochloride or MMF).mp. (10890)
12	(cellcept or mycophenolic acid or morpholinoethyl ester or mycophenolate sodium or RS 61443 or RS-61443 or mycophenolate mofetil or Mycophenolate mofetil hydrochloride or MMF).mp. (10924)
13	cyclosporine/ (26578)
14	(cyclospori$ or ciclospori$ or neoral or sandimmu$ or sandimmun-neoral or gengraf or CyA-NOF or CyA NOF or CsA-Neoral or CsA Neoral or CsANeoral or OL 27-400 or OL 27 400 or OL 27400 or OLO400 or OLO-400 or OLO 400).mp. (53257)
15	tacrolimus/ (13010)
16	(tacrolimus or Prograf or Prograft or Advagraf or FK-506 or FK 506 or FK506 or FR-900506 or FR 900506 or FR900506 or Fujimycin).mp. (20710)
17	5 or 6 or 7 or 8 or 9 or 10 (32061)
18	5 or 6 or 7 or 8 or 9 or 11 (32533)
19	5 or 6 or 7 or 8 or 9 or 12 (32558)
20	13 or 14 or 15 (61565)
21	17 and 20 (10410)
22	18 and 20 (10480)
23	19 and 20 (10495)
24	4 and 17 (1683)
25	4 and 18 (1694)
26	4 and 19 (1698)
27	(editorial or letter or news).pt. (1425861)
28	24 and 27 (45)
29	25 and 27 (45)
30	26 and 27 (45)
31	24 not 28 (1638)
32	25 not 29 (1649)
33	26 not 30 (1653)
34	limit 31 to humans (1475)
35	limit 34 to yr="1990 -Current" (1323)
36	limit 32 to human (1484)

37	limit 36 to yr="1990 -Current" (1332)
38	limit 33 to humans (1487)
39	limit 38 to yr="1990 -Current" (1335)

Table R27: Embase search string comparison including 'or' and the 'mycophenolate sodium' term

Embase Search String	
1	liver graft/ or liver transplantation/ (74250)
2	(liver$ adj3 (transplant$ or graft$)).ti,ab. (66751)
3	(hepatic adj3 (transplant$ or graft$)).ti,ab. (3366)
4	1 or 2 or 3 (83075)
5	everolimus/ (14247)
6	(everolimus or RAD-001 or "RAD 001" or RAD001 or certican or zortress or afinitor or votubia) {Including Related Terms} (666)
7	Azathioprine/ (62363)
8	(azathioprin$ or azothioprin$ or aprin or azap or azasan or azimune or azoprine or azoran or immuzat or imuran or immuran or imurel or thiazprine or transimmune or zinothin or zymurine).mp. (64048)
9	mycophenolic Acid/ (9774)
10	mycophenolic acid 2 morpholinoethyl ester/ (35294)
11	(cellcept or mycophenolic acid morpholinoethyl ester or RS 61443 or RS-61443 or mycophenolate mofetil or Mycophenolate mofetil hydrochloride or MMF).mp. (16017)
12	(cellcept or mycophenolic acid or morpholinoethyl ester or RS 61443 or RS-61443 or mycophenolate mofetil or Mycophenolate mofetil hydrochloride or MMF).mp. (45452)
13	(cellcept or mycophenolic acid or morpholinoethyl ester or mycophenolate sodium or RS 61443 or RS-61443 or mycophenolate mofetil or Mycophenolate mofetil hydrochloride or MMF).mp. (45456)
14	cyclosporine/ (62593)
15	(cyclospori$ or ciclospori$ or neoral or sandimmu$ or sandimmun-neoral or gengraf or CyA-NOF or CyA NOF or CsA-Neoral or CsA Neoral or CsANeoral or OL 27-400 or OL 27 400 or OL 27400 or OLO400 or OLO-400 or OLO 400).mp. (124130)
16	tacrolimus/ (53509)
17	(tacrolimus or Prograf or Prograft or Advagraf or FK-506 or FK 506 or FK506 or FR-900506 or FR 900506 or FR900506 or Fujimycin).mp. (57333)
18	or/5-11 (105297)
19	5 or 6 or 7 or 8 or 9 or 10 or 12 (105616)
20	5 or 6 or 7 or 8 or 9 or 10 or 13 (105619)
21	or/14-17 (151707)
22	18 and 21 (56631)
23	19 and 21 (56656)
24	20 and 21 (56658)
25	4 and 18 (8545)
26	4 and 19 (8551)
27	4 and 20 (8551)
28	25 and (editorial or letter or news).pt. (365)
29	26 and (editorial or letter or news).pt. (365)
30	27 and (editorial or letter or news).pt. (365)
31	25 not 28 (8180)
32	26 not 29 (8186)

33	27 not 30 (8186)
34	limit 31 to humans (7727)
35	limit 34 to yr="1990 -Current" (7563)
36	limit 32 to humans (7731)
37	limit 36 to yr="1990 -Current" (7567)
38	limit 33 to humans (7731)
39	limit 38 to yr="1990 -Current" (7567)

Table R28: Cochrane Library search string comparison including 'or' and the 'mycophenolate sodium' term

Cochrane Library	
1	MeSH descriptor: [Transplantation] explode all trees]
2	Liver:ti,ab,kw
3	Hepatic:ti,ab,kw
4	2 or 3
5	1 and 4
6	everolimus or RAD-001 or "RAD 001" or RAD001 or certican or zortress or Certican or votubia
7	MeSH descriptor: [Azathioprine] explode all trees
8	azathioprin or azathioprine or azothioprin or azothioprine or aprin or azap or azasan or azimune or azoprine or azoran or immuzat or imuran or immuran or imurel or thiazprine or transimmune or zinothin or zymurine
9	MeSH descriptor: [Mycophenolic Acid] explode all trees
10	CellCept or Mycophenolic acid morpholinoethyl ester or RS 61443 or RS- 61443 or mycophenolate mofetil or Mycophenolate mofetil hydrochloride or MMF
11	CellCept or Mycophenolic acid or morpholinoethyl ester or RS 61443 or RS- 61443 or mycophenolate mofetil or Mycophenolate mofetil hydrochloride or MMF
12	CellCept or Mycophenolic acid or morpholinoethyl ester or RS 61443 or RS- 61443 or mycophenolate mofetil or Mycophenolate mofetil hydrochloride or MMF or mycophenolate sodium
13	7 or 8 or 9 or 10 or 11 or 12
14	MeSH descriptor: [Cyclosporine] explode all trees
15	Cyclosporin or ciclosporin or cyclosporine or ciclosporine or Neoral or Sandimmu$ or Sandimmun-Neoral or Gengraf or CyA-NOF or CyA NOF or CsA-Neoral or CsA Neoral or CsANeoral or OL 27-400 or OL 27 400 or OL 27400 or OLO400 or OLO-400 or OLO 400
16	MeSH descriptor: [Tacrolimus] explode all trees
17	tacrolimus or Prograf or Prograft or Advagraf or FK-506 or FK 506 or FK506 or FR-900506 or FR 900506 or FR900506 or Fujimycin
18	14 or 15 or 16 or 17
19	(5 and 13 and 18) from 1990 to 2013

Table R29: DARE search string comparison including 'or' and the 'mycophenolate sodium' term

DARE	
1	liver or hepatic
2	transplant or transplantation or graft or grafting
3	everolimus or RAD-001 or "RAD 001" or RAD001 or Certican or Zortress or Certican or votubia or azathioprin or azathioprine or azothioprin or azothioprine or aprin or azap or azasan or azimune or azoprine or azoran or immuzat or imuran or immuran or imurel or thiazprine or transimmune or zinothin or zymurine or CellCept or Mycophenolic acid morpholinoethyl ester or RS 61443 or RS- 61443 or mycophenolate mofetil or Mycophenolate mofetil hydrochloride or MMF
4	1 and 2 and 3
OR	
1	liver or hepatic
2	transplant or transplantation or graft or grafting
3	everolimus or RAD-001 or "RAD 001" or RAD001 or Certican or Zortress or Certican or votubia or azathioprin or azathioprine or azothioprin or azothioprine or aprin or azap or azasan or azimune or azoprine or azoran or immuzat or imuran or immuran or imurel or thiazprine or transimmune or zinothin or zymurine or CellCept or Mycophenolic acid or morpholinoethyl ester or RS 61443 or RS- 61443 or mycophenolate mofetil or Mycophenolate mofetil hydrochloride or MMF
4	1 and 2 and 3
OR + Soduim	
1	liver or hepatic
2	transplant or transplantation or graft or grafting
3	everolimus or RAD-001 or "RAD 001" or RAD001 or Certican or Zortress or Certican or votubia or azathioprin or azathioprine or azothioprin or azothioprine or aprin or azap or azasan or azimune or azoprine or azoran or immuzat or imuran or immuran or imurel or thiazprine or transimmune or zinothin or zymurine or CellCept or Mycophenolic acid or morpholinoethyl ester or RS 61443 or RS- 61443 or mycophenolate mofetil or Mycophenolate mofetil hydrochloride or MMF or mycophenolate sodium
4	1 and 2 and 3

C3. **Priority Question.** Please clarify why the Company submission has not used free text search terms for the 'transplantation' concept in their search of CENTRAL and CDSR.

Including the free text term of transplantation alone in the CENTRAL and CDSR would return over 3,000 hits, most of which would not be relevant to the study population. As we included free text terms for the comparators of interest, in combination with the MeSH term for transplantation, this was considered sufficient. Also, the free text terms considered in Medline and Embase were likely to capture any relevant studies.

C4. **Priority Question.** Please confirm the data parameters of the resources searched (i.e. OVID MEDINE 1946 to September Week 4 2014).

The date parameters for the searches are:

- OVID MEDLINE 1946 to August Week 3 2014
- Embase 1988 to week 42 2014
- Cochrane and all other databases: from inception to week 42 2014

C5. Please confirm precisely how the searches were limited to human only populations (taking the MEDLINE clinical effectiveness searches as an example, line 22, p252 of the submission).

The limit for human was implemented using the search filter in Ovid for human studies.

C6. **Priority Question.** In the first paragraph of page 159, the Company submission states that "no further changes in this clinical outcome were assumed". Please clarify which outcome you are referring to?

The first paragraph in section 7.3.7 refers to overall survival. However, Novartis would like to clarify that the de novo cost-effectiveness model did not use overall survival information from the NMA.

C7. Please explain the rationale behind the selection of interval ranges used for probabilistic sensitivity analyses (PSA).

Where possible, 95% confidence (or credible) intervals were used from the literature or the NMA. If this data was not available (e.g. for utilities, and some unit costs), a plus or minus 20% approach was chosen.

C8. **Priority Question.** Throughout the submission 12 month, 24 and 36 month data are referred to. However, only 12 month data are included in the economic analysis. 24 and 36 month data could have been used on different occasions, for example to validate model estimates or to obtain adverse events data. Please explain why these longer-term data have not been used at all and also why they are not consistently presented in the clinical section.

Data at 24 and 36 months was very limited. Only key outcomes such as overall survival and graft survival were considered in the NMA for 24 months, though the information was not necessarily consistent with the 12 month outcomes (See question A17). Therefore, to ensure consistency throughout the economic model, Novartis used only 12 month outcomes.

C9. **Priority Question.** The Company submission highlights that one of the limitations of the evidence base is the UK comparator dose. It also states that a blood concentration of <5ng/mL would be considered low-dose tacrolimus in the UK. The H2304 12 month study reports a blood concentration between 3 and 5ng/ml however. Please clarify whether the submission is referring to the comparator studies. Please also clarify the implications of this limitation for the results presented in terms of everolimus cost-effectiveness.

Our understanding of current clinical practice is that UK tacrolimus dosing for both everolimus and standard tacrolimus containing regimens will tend to aim toward the lower range of the blood concentrations stated (3-5 ng/ml for everolimus and 5-20ng/ml for standard tacrolimus). The mean tacrolimus blood concentration for the Europe region sub-group in the H2304 study was [redacted] ng/ml for the everolimus arm and [redacted] ng/ml tacrolimus control arm at 12 months.

It is difficult to then speculate as to the potential implications for everolimus cost-effectiveness. H2304 demonstrated a statistically significant difference in renal function of 8.5ml/min/1.73m^2 at 12 months between the everolimus regimen and the tacrolimus control arm based on the respective target tacrolimus blood concentrations discussed previously. For the Europe region

sub-group the eGFR difference was [redacted] ml/min/1.73m^2 in favour of everolimus (p = 0.009) with the mean 12 month tacrolimus trough blood concentrations stated above. Clinical evidence of CNI-related nephrotoxicity is undisputed, but to relate this to relatively small changes in CNI (tacrolimus) blood concentration is not possible due to the complex number of factors influencing the development of any potential nephrotoxicity such as duration of exposure, patient characteristics and co-morbidities etc. This therefore means that it is not possible to consider implications on everolimus cost-effectiveness with any degree of certainty beyond assuming that a lower tacrolimus dose would possibly be beneficial with respect to preservation of renal function of either an everolimus regimen or a 'standard' tacrolimus regimen. If a lower tacrolimus blood concentration in the everolimus arm led to a greater differential in the favour of everolimus in terms of renal function then cost-effectiveness may move more favourably toward everolimus plus reduced dose tacrolimus.

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