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18 March 2015

Dear Mr. Boysen,

Re: Everolimus for preventing organ rejection in liver transplantation [ID662] – Appraisal Consultation Document

Thank you for your letter dated 18th February 2015 inviting comments on the Appraisal Consultation Document (ACD) for the above appraisal.

Novartis are encouraged that NICE has recognised that everolimus plus reduced-dose tacrolimus provides a valuable and innovative alternative to current treatment, as it allows earlier reduction in the dose of tacrolimus compared to mycophenolate mofetil or azathioprine to achieve better preservation of renal function in patients post-liver transplant. Naturally we are disappointed that NICE has not recommended everolimus at this stage.

Novartis would like to thank NICE for the opportunity to submit further evidence in order to demonstrate improved stability of the model and robustness of cost-effectiveness results for everolimus with reduced-dose tacrolimus in prevention of organ rejection in liver transplantation. All cost-effectiveness results in this response are based on the list price of everolimus (excluding VAT).

Our comments and further evidence are provided in response to the standard four questions on which NICE have stated they are interested in receiving comments (page 1 of the ACD). The additional model analyses are provided in Section I.A), as new evidence in response to the question “Has all of the relevant evidence been taken into account?” Comments on the ACD are provided in Section I.B) and I.C) of the response.

We hope the additional evidence provided within this response will increase confidence in the robustness and reliability of the ICERs compared to our original submission. The cost-effectiveness results should also be considered in the context of further benefits not captured in the modelling, such as the potential anti-tumour effects of everolimus in patients post-liver transplant as discussed by the clinical expert at the Committee meeting (Section 4.2 of ACD).

Everolimus represents an innovative treatment that is highly valued by patients, patient groups and clinicians for its potential to preserve renal function in patients post-transplant through early reduction in tacrolimus dosing. This population currently faces a high unmet need, as in current UK practice, optimal reduction in tacrolimus levels is not consistently being achieved. We ask NICE to consider our response in this context.

If you require clarification on any aspects of our response, please do not hesitate to contact me.

Yours sincerely,

[redacted]

[redacted]

Novartis Pharmaceuticals UK Ltd

The structure of our response to the NICE Appraisal Consultation Document is detailed in the table of contents below.

Table of Contents

Executive Summary

In this response to the NICE ACD for the appraisal of everolimus in the prevention of organ rejection in liver transplantation, Novartis is submitting new evidence for the Committee's consideration. This new evidence consists of a revised cost-effectiveness analysis based on recommendations from the Evidence Review Group (ERG) assessment of the model. Novartis also provides comments on various topics raised in the ACD, notably the generalisability of the pivotal H2304 trial and model results to clinical practice.

By addressing the technical inaccuracies and preferred assumptions by the ERG in the model, as well as increased the number of simulations to 40,000, we have substantially improved the reliability and stability of the model results. This results in incremental cost-effectiveness ratio (ICER) ranges of £103,373 to £104,782 for everolimus plus reduced tacrolimus versus azathioprine plus standard tacrolimus, and ICER ranges of £166,062 to £176,604 for everolimus plus reduced tacrolimus versus mycophenolate mofetil plus standard tacrolimus. The variation between model runs has also substantially reduced to 1.34%-5.97% which is lower than the variation observed with the original model results. Model scenarios were run using the revised model to test impact on the ICERs.

In addition to providing this revised cost-effectiveness analysis, we address one of the Committee's main concerns regarding the generalisability of the H2304 trial as well as the model results to clinical practice in the UK, with regards to the reduction of tacrolimus dosing in patients with liver transplant. In H2304, [redacted] of patients in the everolimus plus reduced tacrolimus arm of H2304 reached a tacrolimus trough level of ≤ 5 ng/mL by month 12, with a median and mean tacrolimus blood concentration of [redacted] and [redacted], respectively. Of the limited published evidence that exists, other studies with a 'reduced' tacrolimus treatment arm in combination with immunosuppressive therapy do not demonstrate as low tacrolimus trough levels as the H2304 study (Rodríguez-Perálvarez 2012).

Furthermore, although the target for low-dose tacrolimus is ≤ 5 ng/mL, the available evidence suggests that in practice, clinicians are reluctant to reduce tacrolimus dosing due to safety concerns and potential risk of acute rejection. Also, as discussed by the clinical expert at the Appraisal Committee meeting, early reduction of tacrolimus trough levels below 5 ng/mL is currently not being achieved consistently in clinical practice (Section 4.2 of ACD), so the successful reduction of tacrolimus trough levels with everolimus represents an effective treatment option which fulfils this unmet need. Overall, the H2304 study demonstrates that reducing tacrolimus dosing in combination with everolimus is an effective and well-tolerated option for patients with a liver transplant.

We ask that the NICE Committee takes into account this new evidence when formulating a recommendation for everolimus in liver transplantation.

I. Has all of the relevant evidence been taken into account?

Novartis has received permission to submit new evidence at this stage in the appraisal process for the Committee to consider. This new evidence is generated from a revised cost-effectiveness model which is described in detail in Section A). The revised analysis is also used to inform and support Novartis' main comments on the ACD in Section B). Section C) provides a summary of minor wording changes and a factual accuracy check for the ACD and Premeeting Briefing (PMB).

A) Revised cost-effectiveness analysis

1) Amendments to cost-effectiveness model

The patient simulation model developed by Novartis to evaluate the cost-effectiveness of everolimus with reduced-dose tacrolimus was revised based on the recommendations outlined in the ERG report. Table 1 below provides a list of amendments to the revised cost-effectiveness model and specific references in the ERG report. Please see Appendix A**:** **Detailed description of model changes** for further detail on how these changes were implemented in the model including specific sheet and cell references in the Excel model.

Table 1: Full list of amendments to revised cost-effectiveness model

No.	Original model assumption	Amendment in revised model	Comments	Document reference
1	Standard TAC estimate from NMA used to inform renal efficacy inputs of model (Absolute decrease in eGFR at 12 months = 31.6)	Renal efficacy data from NMA for MMF plus 'reduced' TAC arm used in the MMF arm of the economic model instead of the standard TAC estimate. The same value was used for the AZA arm of the model as the renal dysfunction is determined by the levels of TAC (and is not dependent on the concomitant drug)	Novartis accepts the ERGs comments that the MMF + 'reduced' TAC arm of the NMA is closer to standard TAC dosing (using H2304 study and UK clinical practice as reference) so has replaced the renal efficacy data in the model with the NMA output for the MMF + 'reduced' TAC arm	ERG report: Page 113-114 ; Section 6.1, page 135
2	Prograf price (£1.61 per mg) used as tacrolimus cost in model	Replaced Prograf price for cost of tacrolimus in model with average brand price calculated by ERG	We understand that the majority of liver centres in the UK use Prograf instead of other brands of tacrolimus or generics. However to be conservative, we will apply the average brand price calculated by the ERG in the revised model	ACD: Section 3.54, p. 22 ERG report: Section 6.1
3	Adverse event costs associated with everolimus were being applied for all 3 months in the first cycle	Everolimus adverse event costs have been adjusted so they are only applied for 2 months (instead of 3 months) in first cycle, as	Novartis accepts the ERG's suggestion and has updated this in the revised analysis, noting that the original assumption was	ERG report: Section 6.1

		everolimus therapy starts 30 days after transplantation	conservative as additional costs were being applied for everolimus in first cycle	
4	Time horizon was set to 80 years	Shorten time horizon to 40 years	As 100% of patients were dead by 40 years in the model, the time horizon has been shortened to 40 years	ACD: Section 3.41
5	Baseline proportions were being used as progression rates of renal disease in the renal sub-model.	Renal progression rates were re-calculated using the correct rate-probability conversion equation to generate correct risk of progression to subsequent CKD stages per 3-monthly cycle	Novartis accepts this correction and has amended in the revised cost-effectiveness model	ERG report, Table 45
6	Error in transition probability formulae	Correction of transition probability formulae allocating patients to acute rejection health state in model	Novartis accepts this correction and has amended in the revised cost-effectiveness model	ERG report p. 97-100
7	Incorrect calculation of transition probabilities	Calculation of transition probabilities from SPT to AR at 9 months and probability of SPT to MCR at month 13+ using correct rate-probability conversion equation	Novartis accepts this correction and has amended in the revised cost-effectiveness model	ERG report p.108-110
8	Negative eGFR values at baseline	Correction of estimation of baseline eGFR levels so no patients start with negative levels of eGFR	Novartis accepts this correction and has amended in the revised cost-effectiveness model	ERG report, p. 113
9	Discovered 10 ‘missing’ cycles in renal sub-mode	Corrected incorrect formula in renal sub-model leading to 10 ‘missing’ cycles	Novartis accepts this correction and has amended in the revised cost-effectiveness model	ERG report, p. 130
10	Previously cost of eGFR-TK mutation test (£150) was incorrectly used as proxy for eGFR test	Cost of eGFR test in renal sub-model has been changed to £2.50, based on the CKD costing template which states that 1 cystatin C test is needed per person to assess eGFR (National Institute for Health and Care Excellence 2014)	Novartis accepts this correction and has amended in the revised cost-effectiveness model	ERG Clarification questions, B12
11	AE disutility of MMF was incorrectly being assigned to AZA, and ‘dummy’ AE disutility was incorrectly being assigned to MMF	AE disutilities associated with MMF and AZA comparators correctly assigned	Following the ERG report, a further check performed on the model revealed an additional error in the assignment of AE disutility for MMF and AZA which has now been corrected	N/A

AE: Adverse event; AR: Acute rejection; AZA: Azathioprine; eGFR: estimated glomerular filtration rate; MCR: Mild chronic rejection; MMF: Mycophenolate mofetil; NMA: Network meta-analysis; SPT: Stable post-transplant; TAC: tacrolimus

2) Scenario analyses performed

In order to explore uncertainty of inputs and structural assumptions of the revised cost-effectiveness model described in Section A) 1) as well as to address the counterintuitive scenario results in the original submission, a series of scenario analyses were re-run with the revised model. Table 2 below provides a list of the scenario analyses, several of which were performed in the original submission but have been re-run with the revised cost-effectiveness model. One of the scenario analyses is new and has been included based on comments from the ERG report, as shown in the table below.

Table 2: Scenario analyses performed with revised cost-effectiveness model

Scenario	Performed in original submission?	Comments	Reference
Change in baseline eGFR from 81 mL/ min per 1.73 m2 to 60mL/min per 1.73 m2	Yes	This scenario was performed in the original submission to test the impact on ICERs with baseline eGFR more reflective of patient population, according to clinical expert	ACD: Section 3.62
MCR state removed from core hepatic model	Yes	Although the Committee concluded that the MCR state was clinically important (Section 4.8 of ACD), the original 'no-MCR state' scenario was re-run with the revised model to test impact on ICER	ACD: Section 3.59
'Fixed' baseline characteristics scenario originally run by ERG to test stability of model	Yes	This scenario was performed by the ERG on the original model in order to assess stability yet resulted in widely varying ICERs.	ACD: Section 3.68
Utilities for AR, ASRR and MCR states adjusted to be lower than SPT state utility	No	This new scenario was added in the response to explore the impact on ICERs when lowering utility for hepatic model health states other than SPT, to address the Committee comments from the Appraisal Committee meeting	ACD: Section 4.10

AR: Acute rejection; AZA: Azathioprine; eGFR: estimated glomerular filtration rate; MCR: Mild chronic rejection; MMF: Mycophenolate mofetil; NMA: Network meta-analysis; SPT: Stable post-transplant; TAC: tacrolimus

3) Base case results from revised model

Two separate runs of the cost-effectiveness model were performed, at 40,000 simulations each in order to improve the stability of the model results. The base case results are shown in

Table 3 and

Table **4**. Although mycophenolate mofetil and azathioprine are considered standard immunosuppressive therapies in the UK, as defined in the final NICE scope, we understand that the relative usage of these two regimens varies between liver centres in the UK. Section B)1) below provides a detailed interpretation of the base case results.

Table 3: Deterministic base-case results with revised cost-effectiveness model – Run 1 (40,000 simulations)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline* (QALYs)	ICER (£) incremental (EVR vs AZA) (QALYs)
MMF + standard TAC	74,258	8.94	3.72					
AZA + standard TAC	73,112	8.52	3.55	-1,146	-0.417	-0.167	6,844	
EVR + reduced TAC	114,593	9.44	3.94	40,335	0.497	0.23	176,604	104,782

*Baseline is MMF + standard TAC; AZA: Azathioprine; EVR: Everolimus; ICER, incremental cost-effectiveness ratio; MMF: Mycophenolate mofetil; LYG, life years gained; QALYs, quality-adjusted life years; TAC: tacrolimus

Table 4: Deterministic base-case results with revised cost-effectiveness model – Run 2 (40,000 simulations)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline* (QALYs)	ICER (£) incremental (EVR vs AZA) (QALYs)
MMF + standard TAC	74,222	8.93	3.71					
AZA + standard TAC	73,013	8.54	3.55	-1,208	-0.387	-0.16	7,611	
EVR + reduced TAC	114,490	9.47	3.95	40,268	0.545	0.24	166,062	103,373

*Baseline is MMF + standard TAC; AZA: Azathioprine; EVR: Everolimus; ICER, incremental cost-effectiveness ratio; MMF: Mycophenolate mofetil; LYG, life years gained; QALYs, quality-adjusted life years; TAC: tacrolimus

4) Scenario analysis results from revised model

Table 5 to

Table 9 demonstrate the results of the scenario analyses using the revised cost-effectiveness model. The 'fixed' baseline characteristics scenario was run twice to test the stability of the model. Appendix B**: Instructions on running model scenarios** provides instruction on running scenarios in the model.

Table 5: Change in baseline eGFR - Scenario results with revised cost-effectiveness model (40,000)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline* (QALYs)	ICER (£) incremental (EVR vs AZA) (QALYs)
MMF + standard TAC	103,322	8.39	3.36					
AZA + standard TAC	101,095	7.96	3.20	-2,226	-0.42	-0.16	13,680	
EVR + reduced TAC	136,925	8.73	3.53	33,603	0.35	0.17	197,404	107,618
*Baseline is MMF + standard TAC; AZA: Azathioprine; EVR: Everolimus; ICER, incremental cost-effectiveness ratio; MMF: Mycophenolate mofetil; LYG, life years gained; QALYs, quality-adjusted life years; TAC: tacrolimus								

Table 6: Removal of MCR state - Scenario results with revised cost-effectiveness model (40,000 simulations)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline* (QALYs)	ICER (£) incremental (EVR vs AZA) (QALYs)
MMF + standard TAC	76,314	9.34	3.81					
AZA + standard TAC	74,214	8.77	3.60	-2,100	-0.58	-0.22	9,785	
EVR + reduced TAC	117,705	9.90	4.05	41,390	0.55	0.24	172,893	95,794
*Baseline is MMF + standard TAC; AZA: Azathioprine; EVR: Everolimus; ICER, incremental cost-effectiveness ratio; MMF: Mycophenolate mofetil; LYG, life years gained; QALYs, quality-adjusted life years; TAC: tacrolimus								

Table 7: 'Fixed' baseline characteristics - Scenario results with revised cost-effectiveness model - Run 1 (40,000 simulations)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline* (QALYs)	ICER (£) incremental (EVR vs AZA) (QALYs)
MMF + standard TAC	55,275	8.00	3.37					
AZA + standard TAC	54,152	7.67	3.24	-1,123	-0.33	-0.13	8,492	
EVR + reduced TAC	96,030	8.32	3.50	40,755	0.32	0.13	320,637	161,462
*Baseline is MMF + standard TAC; AZA: Azathioprine; EVR: Everolimus; ICER, incremental cost-effectiveness ratio; MMF: Mycophenolate mofetil; LYG, life years gained; QALYs, quality-adjusted life years; TAC: tacrolimus								

Table 8: 'Fixed' baseline characteristics - Scenario results with revised cost-effectiveness model - Run 2 (40,000 simulations)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline* (QALYs)	ICER (£) incremental (EVR vs AZA) (QALYs)
MMF + standard TAC	54,888	7.95	3.35					
AZA + standard TAC	53,810	7.62	3.22	-1,078	-0.33	-0.13	8,056	
EVR + reduced TAC	94,581	8.23	3.47	39,693	0.28	0.12	334,139	161,411
*Baseline is MMF + standard TAC; AZA: Azathioprine; EVR: Everolimus; ICER, incremental cost-effectiveness ratio; MMF: Mycophenolate mofetil; LYG, life years gained; QALYs, quality-adjusted life years; TAC: tacrolimus								

Table 9: Utility difference in hepatic model health states - Scenario results with revised cost-effectiveness model (40,000 simulations)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline* (QALYs)	ICER (£) incremental (EVR vs AZA) (QALYs)
MMF + standard TAC	73,873	8.87	3.68					
AZA + standard TAC	72,464	8.46	3.51	-1,409	-0.41	-0.16	8,533	
EVR + reduced TAC	113,923	9.39	3.91	40,050	0.53	0.23	171,116	103,858
*Baseline is MMF + standard TAC; AZA: Azathioprine; EVR: Everolimus; ICER, incremental cost-effectiveness ratio; MMF: Mycophenolate mofetil; LYG, life years gained; QALYs, quality-adjusted life years; TAC: tacrolimus								

5) Results of probabilistic sensitivity analysis in revised model

Due to time constraints and the runtime of the model, it was not possible to perform a probabilistic sensitivity analysis with the revised version of the model.

B) Novartis main comments on the ACD

1) Reliability and stability of cost-effectiveness model

Base case results

Novartis recognises the concerns raised by the Committee and the ERG regarding the stability of the cost-effectiveness model and the resulting lack of confidence in the robustness of the ICERs from the original submission. We understand the model was complex, and appreciate the efforts of the ERG to review the model.

In order to address the concerns of the ERG and the Committee, we have revised the model and have corrected identified technical errors as well as updated various assumptions in the model based on recommendations from the ERG which we believe has increased the reliability of the model results. We have also increased the number of simulations to 40,000 to increase the stability of results. The resulting two runs of the base case cost-effectiveness analysis are shown in

Table 3 and

Table **4** above. A summary of the cost per QALY gained for both runs of the base case analysis compared with the original submission results are shown in Table 10 below to demonstrate how stability in the model has improved since the original submission.

Table 10: Summary of base case ICERs (£ cost per QALY gained) for two individual runs of revised model

Comparison	ICER (£) Cost per QALY gained		Absolute difference (£) Run 1 vs. Run 2	% Change Run 1 vs. Run 2
	Run 1	Run 2		
Original model submitted to NICE (10,000 simulations)				
EVR + reduced TAC vs. MMF + standard TAC	£110,797[¥]	£123,948	13,151	11.9%
EVR + reduced TAC vs. AZA + standard TAC	£187,842[¥]	£245,191	57,349	30.5%
Revised model at list price (40,000 simulations)				
EVR + reduced TAC vs. MMF + standard TAC	£176,604	£166,062	10,542	5.97%
EVR + reduced TAC vs. AZA + standard TAC	£104,782	£103,373	1,409	1.34%

[¥]ICERs reported in original submission to NICE
AZA: Azathioprine; EVR: Everolimus; ICER: Incremental cost-effectiveness ratio; MMF: Mycophenolate mofetil; QALY: Quality-adjusted life years; TAC: tacrolimus

Variation in the base case ICERs has substantially reduced when compared to the percent change between base case ICERs in the original submission. This reduction in percent variation is largely due to the increase in number of simulations from 10,000 to 40,000 in the revised analysis. Novartis has noted that the variation between ICERs is further reduced when the number of simulations is increased to 100,000, however due to time constraints

and the computational burden of the model, this was not possible to complete for all results in time for inclusion in this response

The ICERs are slightly higher for the comparison of everolimus plus reduced tacrolimus versus the mycophenolate mofetil regimen than versus the azathioprine regimen, as mycophenolate mofetil plus standard tacrolimus is associated with a slightly lower per-cycle rate of acute rejection post 13 months from the NMA (0.6%) compared to everolimus (2.5%) and azathioprine (1.6%). Also the mycophenolate regimen has a more favourable AE-related disutility score (-0.011) compared to azathioprine (-0.015), but not when compared with everolimus (-0.009) which demonstrates the best tolerability profile.

'Fixed' baseline characteristic scenario

In order to further test the stability of the model, we have re-run the ERG's 'fixed' baseline characteristics scenario (Section 3.68 of the ACD) which was originally performed to assess whether variation in results was generated by the simulated patient characteristics or attributable to problems in the model. The cost-effectiveness results of the two 'fixed' baseline characteristics scenario runs using the revised model are shown in

Table **7** and

Table **8** above. A summary of the cost per QALY gained for both runs of this scenario analysis, as well as results of the ERG's original analysis as presented in the ERG report (p. 136) are outlined in

Table **11** below.

Table 11: Summary of ICERs (£ cost per QALY gained) for two individual runs of revised model with 'fixed' baseline characteristics scenario

Comparison	ICER (£) Cost per QALY gained		Absolute difference (£) Run 1 vs. Run 2	% Change Run 1 vs. Run 2
	Run 1	Run 2		
ERG analysis of 'fixed' baseline characteristic scenario using original model (10,000 simulations)				
EVR + reduced TAC vs. MMF + standard TAC	£431,348[¥]	£582,668[¥]	151,320	35.1%
EVR + reduced TAC vs. AZA + standard TAC	Dominant[¥]	£797,558[¥]	N/A	N/A
Revised model at list price (40,000 simulations)				
EVR + reduced TAC vs. MMF + standard TAC	320,637	334,139	13,502	4.21%
EVR + reduced TAC vs. AZA + standard TAC	161,462	161,411	51	0.03%

[¥]ICERs reported in ERG report (p.136)
AZA: Azathioprine; EVR: Everolimus; ICER: Incremental cost-effectiveness ratio; MMF: Mycophenolate mofetil; QALY: Quality-adjusted life years; TAC: tacrolimus

Table **11** clearly shows that the results of this scenario analysis in our revised model demonstrate low variation between the ICERs for both comparisons, as expected when patient baseline characteristics are 'fixed' to the mean value. We still expect some difference between the ICERs, however, due to the variation in model parameters, but this variation has substantially reduced when compared to the original submission.

It is important to note that the aim of this scenario was to demonstrate the stability of the revised model. The higher absolute cost per QALY generated with this scenario is largely driven by the fixed baseline estimated glomerular filtration rate (eGFR) at 81 mL/min/1.73 m^2, which means that all simulated patients in this scenario are starting from a CKD stage that is almost normal. Given that the drop in eGFR per patient in the year post-transplant is directly derived from the expected decrease in eGFR versus baseline from the NMA, patients starting with a baseline eGFR of 81 mL/min/1.73 m^2 do not reach later CKD stages (and associated lower utility scores) as quickly. Therefore, the incremental QALY gain for everolimus plus reduced tacrolimus versus comparators (driven by preservation in renal function) is not as pronounced in this scenario, leading to higher ICERs for both comparisons.

Model scenarios from original submission

Finally we re-ran the key scenarios from the original submission (Scenarios 1 and 4, described in Sections 3.59 and 3.62 of ACD) to address the concerns raised by the ERG in Section 3.66 of the ACD regarding the inconsistent results of the scenario analyses from the original model.

Table **12** below shows a summary of the resulting cost per QALY gained for the revised base case analysis and revised scenario analyses.

Table 12: Summary of base case and scenario ICERs (cost per QALY gained) with revised model

Model run*	ICER (£) Cost per QALY gained	
	EVR + reduced TAC vs. MMF + standard TAC	EVR + reduced TAC vs. AZA + standard TAC
Base case run 1	£176,604	£104,782
Base case run 2	£166,062	£103,373
Mild chronic rejection (MCR) state removed from core hepatic model (Scenario 1 in original submission)	£172,893	£95,794
Change in baseline eGFR from 81 mL/ min per 1.73 m2 to 60mL/min per 1.73 m2 (Scenario 4 in original submission)	£197,404	£107,618

*40,000 simulations were performed for each model run

For the mild chronic rejection (MCR) state removal scenario, there is minimal variation in cost per QALY gained when compared to the base case results. This is due to the small proportion of patients transitioning into the MCR state in the model.

For the scenario where baseline eGFR was reduced from 81 mL/ min per 1.73 m^2 to 60mL/min per 1.73 m^2, the cost per QALY gained was slightly higher for both mycophenolate mofetil and azathioprine comparisons versus the base case results. Total costs were higher and total QALYs were lower across all treatment arms in this scenario. This is due to the high cost and lower utility of CKD stage 5 and subsequent renal transplant, as patients with a lower eGFR at baseline are reaching CKD stage 5 much sooner.

Overall, our revised analysis has demonstrated that the stability and reliability of the cost-effectiveness analysis has greatly improved compared to the original submission. We anticipate that with this new model, the Committee will have greater confidence in the robustness of the ICERs.

2) Generalisability to UK clinical practice

H2304 study

Section 4.4 of the ACD states that, the H2304 trial 'appeared to be relevant to clinical practice in England in that the everolimus with reduced-dose tacrolimus group may have had lower tacrolimus blood trough levels than achieved in current clinical practice, although this remained uncertain'. The ERG also discussed this in Section 3.8.

Novartis acknowledges that there is limited published evidence to suggest patients with liver transplant are achieving tacrolimus trough levels ≤5 ng/mL in current UK clinical practice, which was the clinical expert's opinion of optimally reduced tacrolimus trough levels (Section 4.4 in ACD) and aligns with the target range in the H2304 trial. However, of the limited evidence available, there is a clear trend towards tacrolimus trough levels > 5 ng/mL, even in study arms labelled as 'reduced' dose tacrolimus. Only three randomised controlled trials were identified in the systematic review for the network meta-analysis (NMA) (presented in Section 6.7.2 of the original submission) which included 'reduced-dose' tacrolimus in combination with mycophenolate mofetil as a study arm. No studies evaluating 'reduced-

dose' tacrolimus in combination with azathioprine were identified in the systematic review. None of the patients in the 'reduced' tacrolimus arms of the aforementioned three studies achieved tacrolimus trough levels below 5 ng/mL. A recent systematic literature review, conducted between January 2002 and January 2012, identified 64 relevant studies (32 RCTs and 32 observational studies) which reported tacrolimus usage in liver transplantation (Rodríguez-Perálvarez 2012). A meta-analysis was performed on five of the RCTs (n=917 patients) that included 'reduced' dose versus standard dose tacrolimus in combination with another immunosuppressive agent as study arms (including the three studies identified in our systematic review) which is most closely aligned with the treatment strategies considered in our submission (Rodríguez-Perálvarez 2012). Table 13 below shows the target vs. achieved tacrolimus trough levels from these RCTs. Please note the Benitez 2010 and Yoshida 2005 studies were not considered in the systematic review for the NMA as part of the original submission as they did not fulfil the inclusion criteria for intervention and comparator (see Table 14 in original submission for further detail).

Table 13: Summary of tacrolimus dosing from clinical trials identified in recent systematic literature review including 'reduced' tacrolimus study arm (Rodríguez-Perálvarez 2012)

Study	Country	Comparators	Target TAC trough levels in 'reduced' tacrolimus arm	Mean TAC trough levels achieved in 'reduced' tacrolimus arm
Boudjema 2011¥	France	Standard dose tacrolimus MMF + 'reduced dose' tacrolimus	Week 0-6: ≤10 ng/mL Week 6 to month 7: ≤8 ng/mL Month 7-12: ≤6 mg/mL	Week 48: ~ 7.5 ng/mL*
Neuberger 2009¥	Multiple (including UK)	Standard dose tacrolimus MMF + 'reduced dose' tacrolimus	≤8 ng/mL	Week 2: 8.6 ng/mL 1 month: 8.8 ng/mL 3 months: 9.1 ng/mL 4-6 months 8.4 ng/mL 10-12 months: 7.8 ng/mL
Nashan 2009¥	Multiple (including UK)	MMF + standard dose tacrolimus MMF + 'reduced dose' tacrolimus	5-8 ng/mL	Week 26: 7.8 ng/mL
Benitez 2010	Spain	Standard dose tacrolimus ATG-Frenesius + reduced dose tacrolimus	Month 0-3: 5-12 ng/mL By month 12: <5 ng/mL	10 patients selected as suitable for reduction in tacrolimus dosing reached <5 ng/mL, however late acute rejection occurred in all 10 patients which resulted in premature termination

				of trial
Yoshida 2005	Canada	Daclizumab + MMF + delayed reduced dose TAC MMF + standard dose TAC	4-8 ng/mL	Month 12: 8.6- 9.9 ng/mL

MMF: Mycophenolate mofetil

*Estimated from figure, actual tacrolimus trough levels at week 48 not reported in study

¥Studies also identified in Novartis clinical systematic review for inclusion in network meta-analysis

The one RCT where a select group of suitable patients achieved tacrolimus trough levels <5 ng/mL had to be terminated prematurely as all the patients in the 'reduced' dose tacrolimus arm experienced late acute rejections (Benitez 2010). The reduced tacrolimus dosing reported in this systematic literature review lends further support to the clinical expert's opinion (Section 4.4 of ACD) that reduced tacrolimus trough levels ≤ 5 ng/mL are not consistently achieved in practice.

In contrast, [redacted] of patients in the everolimus plus reduced-dose tacrolimus arm of the H2304 trial achieved a mean tacrolimus trough level within or below the target range of 3-5 ng/mL by month 12 (Hexham 2011). The median tacrolimus trough level of patients in this arm was consistently [redacted] from month 4 onwards in the study (Hexham 2011). By month 12 the median tacrolimus trough level in this arm was [redacted] and the mean was [redacted] (Hexham 2011).

The majority of patients in the reduced-dose tacrolimus plus everolimus arm of H2304 were achieving tacrolimus trough levels ≤ 5 ng/mL by month 12. Considering that we would not expect every patient with a liver transplant to be suitable for reduction of tacrolimus trough levels ≤ 5 ng/mL in clinical practice anyway, evidence suggests that a larger proportion of patients can be managed with reduced tacrolimus trough levels when in combination with everolimus compared to combinations with other therapies. Although the target for low-dose tacrolimus is ≤ 5 ng/mL, the available evidence suggests that in practice, clinicians are reluctant to reduce tacrolimus dosing due to potential risk of acute rejection. The H2304 study demonstrates that reducing tacrolimus dosing in combination with everolimus is an effective and valuable treatment option.

Cost-effectiveness model results

In Section 4.4 of the ACD it is noted that 'there was uncertainty about how any benefit demonstrated in the trial would translate into clinical practice.' In Section 6.10 of the original submission, the applicability of H2304 to UK clinical practice was discussed and a key limitation that was highlighted was the baseline eGFR from H2304. Randomised patients in the H2304 study had a mean eGFR of 81 mL/min/1.73m^2 which is close to a normal eGFR measure (≥ 90 mL/min/1.73m^2). A scenario analysis was performed in the original submission to assess the impact of reducing the baseline eGFR to 60 mL/min/1.73m^2 which

the clinical expert considered more reflective of baseline eGFR values observed in clinical practice in England (Section 4.4 of ACD).

This scenario analysis has been re-run using the revised cost-effectiveness model, and the resulting cost per QALY gained was £197,404 for the comparison against the mycophenolate mofetil regimen and £107,618 for the comparison against the azathioprine regimen, which are slightly higher, yet similar to the base case results. Detailed results are shown in Table 5.

It is important to remember that the key benefits of everolimus are not only that it allows further reduction of tacrolimus dosing compared to other therapies, but also that it allows *earlier* reduction of tacrolimus dosing (as outlined by the clinical expert in Section 4.2 of the ACD) which has been shown to be a key predictor in renal toxicity (Karie-Guigues 2009; Rodríguez-Perálvarez 2012). This means that in order for clinicians to maximise the long-term preservation of renal function in patients with a liver transplant, it would be clinically beneficial to initiate everolimus plus early reduced tacrolimus in patients who already have relatively healthy renal function.

3) Clarification on network meta-analysis

The validity of the network meta-analysis (NMA), used to populate efficacy inputs in the model, has been raised as a concern by both the ERG (Section 3.30) and the Committee (Sections 4.5 and 4.9) throughout the ACD. The key critique of the NMA involves the classification of tacrolimus dosing in the NMA, which was been criticised as not being reflective of UK clinical practice.

We have attempted to address this criticism by following the ERG's recommendation of applying the estimate for decrease in eGFR at 12 months from the MMF plus 'reduced' tacrolimus arm of the NMA, instead of the NMA results from the standard TAC arm which was the assumption in the original model (further detail on page 114 of the ERG report). We acknowledge that the studies informing the MMF plus 'reduced' tacrolimus arm of the NMA could be considered MMF plus standard tacrolimus, as tacrolimus trough levels were consistently > 7.5 ng/mL throughout the duration of the studies. This is also discussed in Section B)2) of this response. The exact tacrolimus trough levels of these studies (Boudjema 2011, Neuberger 2009) are presented in Table 13.

Table **14** below shows the estimate for decrease in renal function at 12 months from the original submission and the updated values in the revised cost-effectiveness analysis presented in this response. The difference in change from baseline eGFR between everolimus regimen and the comparator regimens has been reduced with this assumption in the revised model, which represents a more conservative approach.

Table 14: Estimates for decrease in renal function at 12 months for each treatment from original and revised cost-effectiveness analyses

Treatment	Estimate for decrease in renal function (eGFR) at 12 months (mL/min/1.73m^2)	
	Original submission (based on standard TAC arm of NMA)	Revised model (based on MMF + 'reduced' TAC arm of NMA)
EVR + reduced TAC	-23.1	-23.1
MMF + standard TAC	-31.6	-28.2
AZA + standard TAC	-31.6	-28.2

In addition to the renal efficacy inputs, Novartis investigated the impact of reclassifying tacrolimus dosing in the NMA on the acute rejection efficacy inputs in the model. Therefore, the NMA was re-run using the following criteria:

- Any studies reporting treatment arms which include tacrolimus at trough levels ≤ 5 ng/mL will be re-classified as 'reduced tacrolimus'
- Any studies reporting treatment arms which include tacrolimus at trough levels > 5 ng/mL will be re-classified as 'standard tacrolimus'

Applying the above criteria, the only changes to the network involved two studies previously classified as mycophenolate mofetil plus 'reduced' tacrolimus (Boudjema 2011, Neuberger 2009) which were re-classified as mycophenolate mofetil plus standard tacrolimus. One of the studies eligible for re-classification (Nashan 2009) included a mycophenolate mofetil plus 'reduced' tacrolimus arm compared to mycophenolate mofetil plus standard tacrolimus arm. As a result of the re-classification of tacrolimus dosing, both arms were re-classified as mycophenolate mofetil plus standard tacrolimus, therefore this study had to be excluded from the revised NMA as a study with two identical treatment arms, and no relative effect, could not feasibly inform the NMA.

The results of the revised NMA and the original NMA calculated as probability of acute rejection at different time points are shown in Table 15 below. Appendix C**: Results of original and revised NMA for biopsy-proven acute rejection (BPAR) outcomes at 3, 6 and 12 months** provides further detail on the results of the NMA and how these results were converted to risk of acute probability in the model. Revised network diagrams are shown in Appendix D: **Network diagrams for biopsy-proven acute rejection (BPAR) outcomes at 3, 6 and 12 months from revised NMA**

Table 15: Probability of acute rejection by treatment arm from original and revised NMA results

Results	EVR + reduced TAC	MMF + standard TAC	AZA + standard TAC
Probability of SPT to AR at 0-3 months			

Original NMA	1.9%	11.3%	13.8%
Revised NMA	3.1%	16.3%	20.9%
Probability of SPT to AR at 4-6 months			
Original NMA	3.7%	4.1%	7.5%
Revised NMA	3.5%	1.9%	3.9%
Probability of SPT to AR at 7-9 months			
Original NMA	2.5%	0.6%	1.6%
Revised NMA	4.2%	3.3%	3.8%
Probability of SPT to AR at 10-12 months			
Original NMA	2.5%	0.6%	1.6%
Revised NMA	4.2%	3.3%	3.8%
Probability of SPT to AR at 13+ months			
Original NMA	2.5%	0.6%	1.6%
Revised NMA	4.2%	3.3%	3.8%

Although the probability of acute rejection has changed slightly versus the original model with the re-classification of tacrolimus dosing in the NMA, the risk of acute rejection after year 1 is now more uniform across treatment arms. Unfortunately due to time constraints we have only been able to run an analysis using 10,000 simulations with the revised acute rejection rates included in the model. Results are shown in Table 16 below.

Table 16: Model results with updated acute rejection rates from revised NMA (10,000 simulations)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline* (QALYs)	ICER (£) incremental (EVR vs AZA) (QALYs)
MMF + standard TAC	70,725	8.36	3.51					
AZA + standard TAC	68,887	7.89	3.32	-1,838	-0.47	-0.19	9,673	
EVR + reduced TAC	114,983	9.43	3.94	44,258	1.07	0.43	101,893	73,827
*Baseline is MMF + standard TAC; AZA: Azathioprine; EVR: Everolimus; ICER, incremental cost-effectiveness ratio; MMF: Mycophenolate mofetil; LYG, life years gained; QALYs, quality-adjusted life years; TAC: tacrolimus								

The ICERs in this scenario are slightly lower than the base case results. This is driven by the higher incremental QALYs versus the base case results for the everolimus regimen, as a result of the increased probability of acute rejection for the comparator regimens from the revised NMA output.

4) Health state utilities

Section 4.10 of the ACD outlines the concerns from the Committee regarding the utility values per health states in the hepatic core model. The question was raised whether acute rejection (AR), acute steroid-resistant rejection (ASRR) and MCR health states should be considered asymptomatic, resulting in equivalent utility values to the stable post-transplant (SPT) state in the core hepatic model. As described in Section 7.4.9 of the original

submission, the assumption that these health states are largely asymptomatic was based on input from the clinical experts.

A scenario analysis was performed to assess the impact of assigning a lower utility score to the AR, ASRR and MCR states. The utility values applied to these health states in the scenario was assumed to be the mid-point between the SPT state utility score (0.58) and the utility score associated with severe chronic rejection (0.53) which equals a utility score of 0.555. Table 17 below shows the utility values assigned to hepatic health states in this scenario.

Table 17: Utility scores assigned to hepatic health states in the utility decrement model scenario

Hepatic core model health states	Utility score
Stable post-transplant state	0.58
Acute rejection	0.56
Acute steroid resistant rejection	0.56
Mild chronic rejection	0.56
Graft loss (severe chronic rejection)	0.53
Stable PT via liver re-transplant	0.58

Table 17 above demonstrates the results of the scenario analysis assessing utility decrements for the hepatic model health states. The cost per QALY gained for the mycophenolate mofetil comparison was £171,116 and £103,858 for the azathioprine comparison. These results show that applying a lower utility score to the AR, ASRR and MCR health states in the hepatic model has a minimal impact on cost-effectiveness results. This is due to the relatively low acute rejection risk per cycle for all treatment arms after 1 year in the revised model (2.5%, 1.6% and 0.6% for everolimus, azathioprine, and mycophenolate mofetil regimens, respectively) as well as the relatively small difference in acute rejection risk between treatments.

In Section 4.10, the Committee also raised a concern around the plausibility of a reduction in utility from 0.83 to 0.64, for patients moving from no CKD to CKD stages 1/2 in the renal sub-model. However due to the application of the minimum method for assigning utilities across both the hepatic core model and the renal sub-model (as described in 7.4.9 of the original submission), patients will never be assigned a utility score of 0.83 as the utility scores across all states in the hepatic core model are lower than 0.83.

C) Novartis supplementary comments

In addition to the major comments above, we also have some minor comments regarding the ACD, as follows:

Section number	Comments and/or suggested wording change

3.31	Novartis acknowledges there was an oversight in not including the correct WinBUGS code in the original submission. However, as raised in Issue 21 of the ERG report factual accuracy check, the ERG did not raise this as an issue at the clarification stage, at which stage Novartis would have sent all the codes required for the ERG to run the analysis as we had these available. Additionally, as discussed in Issue 21, we do not understand why the ERG requested more advanced diagnostics such as leverage plots for the NMA at the clarification stages when they had not attempted to re-run the base case analysis for the outcomes.
3.31/4.5	The ERG stated that it was unclear which studies had been included in the NMA for the tBPAR outcome. This was addressed in Issue 22 of the ERG report factual accuracy check. Appendix 14 of the original submission includes Figures 23, 24, 25 which summarise the networks for acute rejection.

We also have some minor comments regarded factual inaccuracies in the Pre-Meeting Briefing, as follows:

Section number	**Factual accuracy comments**
Table 1, Page 6	Under the column 'Comments from the ERG' the following sentence '…the broad term mycophenolate acid could have been used…' should refer to **mycophenolic acid** instead. This was also raised in the factual accuracy check of the ERG report (Issue 7).
4.13	At the end of Section 4.13, the values reported for Kaplan-Meier tBPAR-free probability were actually the proportion of patients with acute rejection. If the intent was to report probability of tBPAR, the sentence should read as follows (bolded text where amended): 'At 12 months, the **probability of tBPAR** was **2.9%** in the everolimus group compared with **7.0%** in the standard dose tacrolimus group, 95% CI for the difference – 8.0 to -0.3; p-value **= 0.035**' Similarly for the 24 month data, the values reported refer to the probability of BPAR not tBPAR. Additionally, only the 97.5% CI are reported in the publication. If the intent was to report probability of tBPAR at 24 months, the sentence should read as follows (bolded text where amended): 'At 24 months, the **probability of tBPAR** was **4.8%** and **7.7%** respectively, **97.5%** CI for the difference **-7.9 to 2.2**; p-value = **0.203**'
4.35	There is an incorrect reference to 24 weeks when it should be referring to months. The sentence should read as follows: 'At 24 **months**, the incidence of new onset diabetes mellitus was higher in the everolimus group…'

II. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The current summaries do not take into account all of the evidence outlined in Section I above; as a result we believe the current summaries cannot be considered complete and reasonable until this additional evidence is taken into account.

III. Are the provisional recommendations sound and basis for guidance to the NHS?

The model amendments and revised cost-effectiveness analyses presented in this response demonstrate the significant improvement in the stability and reliability of the model results, which was a key concern raised by both the ERG and the Committee.

Everolimus with reduced-dose tacrolimus is an efficacious and generally well-tolerated treatment option in the prevention of organ rejection for patients with a liver transplant. Most significantly, everolimus with early reduction in tacrolimus dosing significantly reduces renal impairment as a result of the low tacrolimus trough levels being achieved by patients in this study arm. As discussed by the clinical expert at the first Appraisal Committee meeting, early reduction of tacrolimus trough levels below 5 ng/mL is currently not consistently being achieved in clinical practice, so the successful reduction of tacrolimus trough levels with everolimus represents an effective treatment option which fulfils this unmet need.

Therefore we do not consider the provisional recommendations a sound and suitable basis for guidance to the NHS.

IV. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Novartis cannot identify any significant equality issues with the use of everolimus in liver transplantation.

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Appendix A: Detailed description of model changes

Table 18: Full list of amendments to revised cost-effectiveness model

No.	Amendment in revised model	Sheet and Cell References in Excel model	Description of change
1	Renal efficacy data from NMA for MMF+ 'reduced' TAC arm used in the MMF arm of the economic model instead of the standard TAC estimate. The same value was used for the AZA arm of the model as the renal dysfunction is determined by the levels of TAC (and is not dependent on the concomitant drug).	'Efficacy & Safety' sheet; Cells K15:M15; N15:P15	Base Case, Low and High values for eGFR decrease at 12 months replaced with MMF + 'reduced' TAC arm from NMA for both MMF + TAC and AZA + TAC comparators (-28.2 base case, -32.3 to -24.1)
2	Replaced Prograf price for cost of tacrolimus in model with average brand price calculated by ERG	'Unit Costs' sheet; Cell N65	Prograf cost per mg (£1.61) replaced with average brand price calculated by ERG (£1.30 per mg)
3	Everolimus adverse event costs have been adjusted so they are only applied for 2 months (instead of 3 months) in first cycle, as everolimus therapy starts 30 days after transplantation.	Tab "PLS Calculations ARM1", Cell AG24	Changed from =IF(T24=1,0,((1+VLOOKUP(AB24,Reduction_AEprevalence_EVER,5,FALSE))*Cost_AEs_EVER)) to =IF(T24=1,0,((1+VLOOKUP(AB24,Reduction_AEprevalence_EVER,5,FALSE))*Cost_AEs_EVER))*(2/3)
4	Shorten time horizon to 40 years	'Model Parameters' sheet; Cell J14	Manually input time horizon of 40 years.
5	Renal progression rates were re-calculated using the correct rate-probability conversion equation to generate correct risk of progression to subsequent CKD stages per 3-monthly cycle	'Efficacy & Safety' sheet; Cells H21:P24	Correct rate-probability conversion formula was entered in the cells in this sheet to re-calculate renal progression rates for each treatment arm
6	Correction of transition probability formulae allocating patients to acute rejection health state in model	All PLS Calculation tabs, Cells J28:J183	Changed from =VLOOKUP(W24,To_AR_EVER,(Y24+2),FALSE) to =VLOOKUP(W27,To_AR_EVER,(5),FALSE), which forces the model to apply the same risk of transitioning to this state from year 1 onwards.
7	Calculation of transition probabilities from SPT to AR at 9 months and probability of SPT to MCR at month 13+ using correct rate-probability conversion equation.	'Variables sheet; Cells I196:I198, I211:I213, I226:228 'Model Parameters' sheet; Cell L41	Correct rate-probability conversion calculations entered in the cells in this sheet to re-calculate risk of AR at 9 months and transition to MCR state at month 13+. Amended to correct formula (e.g. =1-EXP(((LN(1-(BPAR_free_6m_MMF-BPAR_free_12m_MMF)))/6)*3))
8	Correction of estimation of baseline eGFR levels so no patients start	"PLS Calculations" sheet, K16; 'Variables'	Amended incorrect value (43.7) in the standard deviation (SD) which

	with negative levels of eGFR	sheet S27	was causing negative baseline eGFR. Replaced with SD of 32.7 from trial.
9	Corrected incorrect formula in renal sub-model leading to 10 'missing' cycles	'PLS Calculations ARM1', AF188	Incorrect formula entered into Cell AF188. Corrected to include the last 10 cycles. Please note this would not have impact on the model as this formula is a tracking value.
10	Cost of eGFR test in renal sub-model has been changed to £2.50, based on the CKD costing template which states that 1 cystatin C test is needed per person to assess eGFR (National Institute for Health and Care Excellence 2014)	'Unit Costs' sheet; Cell H92	Cost of eGFR changed to £2.50 in this cell.
11	AE disutilities associated with MMF and AZA comparators correctly assigned	'Variables' sheet; Cell K70 and K71	Cell K70 correctly linked to AZA AE disutility (Utilities!O40) and cell K71 correctly linked to MMF AE disutility (Utilities!Q40)

AE: Adverse events; AR: Acute rejection; AZA: Azathioprine; eGFR: estimated glomerular filtration rate; MCR: Mild chronic rejection; MMF: Mycophenolate mofetil; NMA: Network meta-analysis; SPT: Stable post-transplant; TAC: tacrolimus

Appendix B: Instructions on running model scenarios

Table 19: Instructions on running model scenarios with the revised model

No.	Amendment in revised model	Sheet and Cell References in Excel model	Instruction
1	Change in baseline eGFR from 81 mL/ min per 1.73 m^2 to 60mL/min per 1.73 m^2	'Model Parameters' sheet; Cell K27	Manually set mean eGFR to 60 60mL/min per 1.73 m^2 In this cell
2	MCR state removed from core hepatic model	'Model Parameters' sheet; Cell L41	Manually set 3-month probability of transition to MCR state to 0%
3	'Fixed' baseline characteristics scenario originally run by ERG to test stability of model	Tab "PLS Calculations ARM1", Cells K10:K16 Tab "PLS Calculations ARM2", Cells K10:K16 Tab "PLS Calculations ARM3", Cells K10:K16	Set single patients starting characteristics equal to corresponding baseline value in Table 4 of the 'Model Parameters' sheet.
4	Utilities for AR, ASRR and MCR states adjusted to be less than SPT state utility	'Utilities' sheet; Cell H12:H14	Input a utility value of 0.555 in these cells. Multiply base case by 95% and 105% to generate low and high values, respectively in Cells I12:I14 and J12:J14

AR: Acute rejection; ASRR: Acute steroid-resistant rejection; eGFR: estimated glomerular filtration rate; MCR: Mild chronic rejection; NMA: Network meta-analysis; SPT: Stable post-transplant

Appendix C: Results of original and revised NMA for biopsy-proven acute rejection (BPAR) outcomes at 3, 6 and 12 months

Table 20: Absolute estimate of BPAR-free at 3 months from original and revised NMA results (fixed effects model)

Intervention	Revised NMA results absolute estimate 95% CrI ranking	Original NMA results absolute estimate 95% CrI ranking
standard TAC	73.0% 69.6% 86.0% 5	81.6% 86.0% 76.2% 6
AZA + CYC	69.8% 52.6% 83.3% 6	79.4% 89.7% 83.2% 7
AZA + standard TAC	79.1% 74.2% 83.3% 3	86.2% 90.6% 83.4% 4
MMF + CYC	75.9% 58.0% 87.7% 4	84.0% 92.8% 88.0% 5
MMF + standard TAC	83.7% 78.7% 92.9% 3	88.7% 92.9% 87.8% 3
MMF + reduced TAC	N/A	90.8% 94.5% 95.3% 2
EVR + reduced TAC	96.9% 89.2% 99.6% 1	98.1% 99.7% 99.6% 1

Table 21: Absolute estimate of BPAR-free at 6 months from original and revised NMA results (random effects model)

Intervention	Revised NMA results absolute estimate 95% CrI ranking	Original NMA results absolute estimate 95% CrI ranking
standard TAC	77.4% 73.2% 81.2% 4	79.2% 74.1% 83.8% 4
AZA + CYC	66.9% 0.1% 100.0% 5	70.6% 0.0% 100.0% 6
AZA + standard TAC	75.2% 0.0% 100.0% 4	78.5% 0.0% 100.0% 5
MMF + CYC	75.0% 0.8% 99.9% 4	75.3% 99.9% 99.9% 5
MMF + standard TAC	81.8% 13.9% 99.2%	84.3% 1.7% 100.0%

	3	4
MMF + reduced TAC	N/A	83.7% 15.5% 99.3% 4
EVR + reduced TAC	93.4% 11.0% 99.9% 1	94.2% 11.4% 99.3% 1

Table 22: Absolute estimate of BPAR-free at 12 months from original and revised NMA results (random effects model)

Intervention	Revised NMA results absolute estimate 95% CrI ranking	Original NMA results absolute estimate 95% CrI ranking
standard TAC	69.1% 65.4% 72.7% 3	75.5% 70.1% 80.3% 5
AZA + CYC	63.8% 48.0% 77.0% 5	72.7% 41.8% 91.9% 5
AZA + standard TAC	67.7% 58.7% 75.6% 4	74.8% 51.4% 89.3% 5
MMF + standard TAC	75.4% 70.3% 79.9% 2	83.8% 63.6% 94.6% 2
MMF + reduced TAC	N/A	80.5% 57.8% 92.4% 3
EVR + reduced TAC	85.2% 74.5% 92.4% 1	88.9% 61.7% 97.5% 1

Calculations for model inputs:

For months 0-3:

To calculate the risk of acute rejection in this time range, the estimate of BPAR-free from Table 20 was subtracted by 100%.

E.g. for everolimus plus reduced tacrolimus, 100% - 96.9% = 3.1%

For months 4-6:

To calculate the risk of acute rejection in this time range, the estimate of BPAR-free from Table 20 was subtracted by the estimate of BPAR-free from Table 21.

E.g. for everolimus plus reduced tacrolimus, 96.9%-93.4% = 3.5%

For months 7-9, 10-12 and 13+:

As there were no NMA results for BPAR-free at 9 months, the probability of BPAR-free from Table 21 was subtracted by the estimate of BPAR-free from

Table 22 to generate a 6-month probability of acute rejection. To convert this into a 3-month probability for inclusion in the model, the following rate-probability conversion was performed.

E.g. for everolimus plus reduced tacrolimus, 93.4%-85.2% = 8.2%

3-month rate = (-1/2)*ln(1-0.082) = 4.28%

3-month probability = 1-exp(-0.0428) = 4.19%

This 3-month probability was applied for months 7-9, 10-12 and from 13 onwards.

Appendix D: Network diagrams for biopsy-proven acute rejection (BPAR) outcomes at 3, 6 and 12 months from revised NMA

Figure 1: Network for BPAR outcomes at 3 months

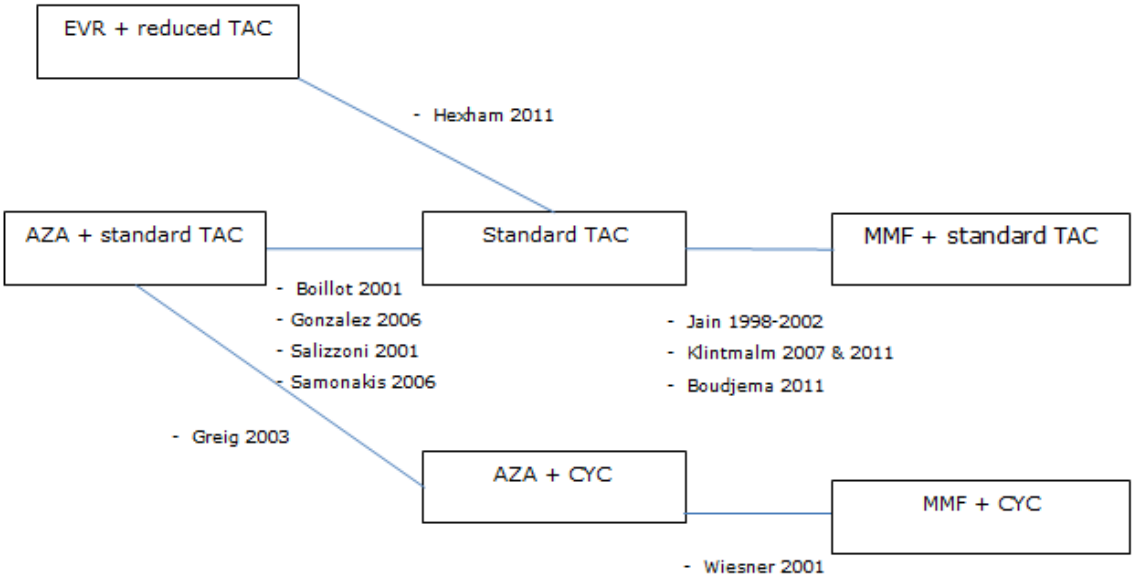

Figure 2: Network for BPAR outcomes at 6 months

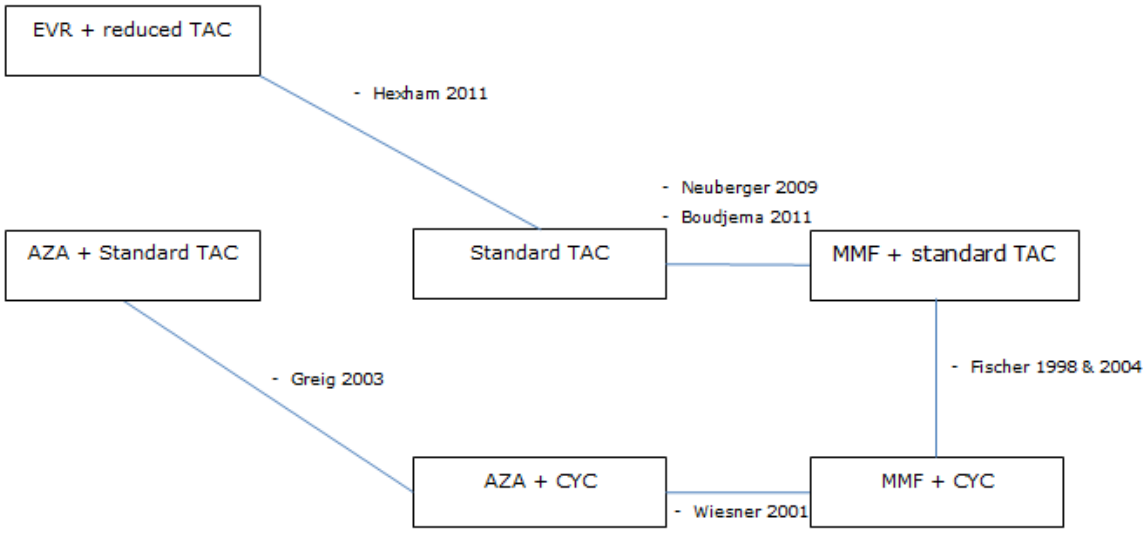

Figure 3: Network for BPAR outcomes at 12 months