Additional analyses

Novartis model re-runs

Table 1. Model updates

Location of update	Change in value/formula
Utilities	
Created new inputs on “QoL” sheet	Regression coefficients for baseline utility: D27: 0.967981 (constant), D28: -0.001807 (age), D29: -0.0001 (age squared), D30: 0.023289 (gender) Utility decrement for health states: D36: 0.277 (haemodialysis), D37: 0.264 (peritoneal dialysis), D43: 0.053 (functioning graft)
Created new calculation columns in “Tx QALYs” and “Comp QALYs” sheets * Calculations are presented for the treatment arm. In the comparator arm, calculations are linked to the comparator sheet	Calculations for background utility: K11:K611 Formula: *QoL!$D$27 + Treatment!D11*QoL!$D$28 + (Treatment!D11^2)*QoL!$D$29 + QoL!$D$30*'Set-Up'!$D$25* Decrement for health status: *L11:L611 = IF(Treatment!Q11="Yes", QoL!$D$43, AVERAGE(QoL!$D$36:$D$37))* Overall utility: *M11:M611 = IF(Treatment!J11="Yes",0,K11-L11)*
Amended QALY calculation column to use these new values	Calculations for total discounted QALYs: F11:F611 New formula: *(M11/12-E11)/((1+'Set-Up'!$D$17)^(C11/12))*
NODAT	
Created new input cells in the “Safety” sheet Converted annual incidence rate to one month probability (in “Safety” sheet) Created NODAT disutility input cell in “QoL”	<u>“Safety”</u>: D41: 4.98% (12 month NODAT incidence for CSA+MMF), D42: 4.98% (12 month NODAT incidence for BAS+CSA+MMF), D43: 4.74% (12 month NODAT incidence for CSA+EVL), D44: 4.66% (12 month NODAT incidence for BAS+CSA+MPS), E41:E44: *1-EXP(LN(1-D41)/12)* (formula linked to appropriate cell for each comparator) <u>“QoL”</u>: D49: 0.06 (utility decrement for NODAT) <u>“Resource use (2)”</u>:

Created NODAT cost input cell in "Resource use (2)"	I41: 1388.92/12 + 694.92/12 + 0.0054*3*365.25/12 (monthly treatment cost)
Created new calculation columns in "Treatment" and "Comparator" sheets Created new calculation columns in "Tx Costs" and "Comp Costs" sheets and updated total discounted cost calculations Created new calculation columns in "Tx QALYs" and "Comp QALYs" sheet and updated total discounted QALY calculations	<u>"Treatment" and "Comparator":</u> *AH11:AH22: RAND()* (random seed for event) *AH23:AH611: 1* (to allow no new NODAT events to occur after one year) AI11:AI611: Cycle 1: *IF(J11="Yes","Died",IF(AH11<Safety!$E$44,"Yes","No"));* Cycle 2+: *IF(J12="Yes","Died",IF(AI11="Yes","Yes",IF(AH12<Safety!$E$44,"Yes","No")))* <u>"Tx Costs" and "Comp Costs"</u> NODAT cost per cycle: *X11:X611= IF(Treatment!AI11="Yes", 'Resource use (2)'!$I$41,0)* Total cost formula: *L11:L611 = SUM(D11:K11)+X11* <u>"Tx QALYs" and "Comp QALYs"</u> NODAT disutility per cycle: *O11:O611 = IF(Treatment!AI11="Yes",QoL!$D$49,0)/12* Total discounted QALY: *F11:F611 = (D11-E11 - O11)/((1+'Set-Up'!$D$17)^(C11/12)*
Costs	
Created new input cells in "Resource use" for drug unit costs Updated input cells in "Resource use (2)" for health state costs, and created new input cells for proportion receiving haemodialysis over time	<u>"Resource use"</u> Drug unit costs: M13: 0.004478 (mycophenolate sodium cost per mg), M14: 0.3774 (mycophenolate mofetil cost per g), M15: 9.9 (everolimus cost per mg), M17: 0.0165 (ciclosporin cost per mg), M19: 842.38*1.964 (total basiliximab cost), M20: 0.003286 (corticosteroid cost per mg) Everolimus month cut-off (for dosing): K25=0, K26=3, K27=6, K28=9, K29=12, K30=24 Everolimus dosing (mg/day) over time: M25=2.97, M26=2.75, M27=2.53, M28=2.6, M29=2.6, M30=2 MMF month cut-off (for dosing): K34=0, K35=3, K36=12 MMF dosing (mg/day) over time: K34=2, K35=1.84, K36=1.67 MPS month cut-off (for dosing): K56=0, K57=3, K58=9 MPS dosing (mg/day) over time: K56=1440, K57=1211, K58=1107 Ciclosporin (with EVL) month cut-off (for dosing): K40=0, K41=12 Ciclosporin (with EVL) dosing (mg/kg/day) over time: K40=3.9, K41=2.1

	Ciclosporin (with MPA) month cut-off (for dosing): K46=0, K47=1, K48=2, K49=3, K50=6, Ciclosporin (with MPA) dosing (mg/kg/day) over time: K46=6.67, K47=4.39, K48=3.06, K49=2.86, K50=2.82 "Resource use (2)" Health state costs: D13: £3,557 (acute rejection), D14: £6,093 (haemodialysis), D15: £6,000 (peritoneal dialysis), D16: £36,966 (re-transplantation) Age cut-offs: H23=18, H24=25, H25=35, H26=45, H27=55, H28=65, H29=75, H30=85 Proportion with haemodialysis for each age: J23=0.791, J24=0.804, J25=0.845, J26=0.843, J27=0.852, J28=0.858, J29=0.89, J30=0.915
Updated drug cost and dialysis calculations in "Tx Costs" and "Comp Costs"	EVL+MMF drug costs: D11 = IF(Treatment!J11="No",(VLOOKUP(C11,'Resource use'!$K$25:$M$30, 3)*'Resource use'!$M$15 + VLOOKUP(C11,'Resource use'!$K$40:$M$41, 3)*LIVE!$C$28*'Resource use'!$M$18 + 'Resource use'!$M$20*'Resource use'!$N$20)*365.25/12,0) CSA+MMF drug costs: D11 = IF(Comparator!J11="No", (VLOOKUP(C11,'Resource use'!$K$34:$M$36, 3)*'Resource use'!$M$14 + VLOOKUP(C11,'Resource use'!$K$46:$M$51,3)*LIVE!$C$28*'Resource use'!$M$18 + 'Resource use'!$O$20)*365.25/12,0) BAS+CSA+MPS drug costs: *D11 = IF(Treatment!J11="No",(VLOOKUP(C11,'Resource use'!$K$56:$M$58,3)*'Resource use'!$M$13 + VLOOKUP(C11,'Resource use'!$K$46:$M$51,3)*'Resource use'!$M$18 + 'Resource use'!$M$20*'Resource use'!$N$20)*365.25/12 + 'Resource use'!M19,0)* *D12 = IF(Treatment!J12="No",(VLOOKUP(C12,'Resource use'!$K$56:$M$58,3)*'Resource use'!$M$13 + VLOOKUP(C12,'Resource use'!$K$46:$M$51,3)*'Resource use'!$M$18 + 'Resource use'!$M$20*'Resource use'!$N$20)*365.25/12, 0)* BAS+CSA+MMF drug costs: *D11= IF(Comparator!J11="No",(VLOOKUP(C11,'Resource use'!$K$34:$M$36, 3)*'Resource use'!$M$14 + VLOOKUP(C11,'Resource use'!$K$46:$M$51,3)*'Resource use'!$M$18 + 'Resource use'!$O$20)*365.25/12 + 'Resource use'!M19,0)* *D12 = IF(Comparator!J12="No",(VLOOKUP(C12,'Resource use'!$K$34:$M$36,3)*'Resource use'!$M$14 + VLOOKUP(C12,'Resource use'!$K$46:$M$51,3)*'Resource use'!$M$18 + 'Resource use'!$M$20*'Resource use'!$N$20)*365.25/12,0)* Dialysis cost calculations

	H11:H611 = IF(Treatment!R11="Yes", (VLOOKUP(ROUNDDOWN(Treatment!D11,0), 'Resource use (2)'!$H$23:$J$30,3)*'Resource use (2)'!$D$14 + (1- VLOOKUP(ROUNDDOWN(Treatment!D11,0), 'Resource use (2)'!$H$23:$J$30,3))*'Resource use (2)'!$D$15)/3, 0)

Table 2. ICERs for EC-MPS vs MMF (with PenTAG NMA inputs, costs and NODAT at one year)

Using PenTAG utility values	Using Novartis utility values
£145,194	£27,327

Table 3. ICERs for EC-MPS vs MMF (using PenTAG clinical inputs and long-term graft survival rates)

	ICER
Using PenTAG long-term graft survival rates	£36,074
Graft survival and PenTAG utility values	£29,254
Graft survival and PenTAG costs	£26,302
Graft survival and PenTAG NODAT	£36,002

Table 4 Analysis of EVL vs MMF (revised base case results)

	Discounted cost		Discounted QALYs		ICER
	Total	**Incremental**	**Total**	**Incremental**	
EVL	£195,411	–	7.07	–	–
MMF	£88,574	£106,838	6.01	1.06	£100,459

Table 5. Analysis of EC-MPS vs MMF, using one-year clinical inputs from the PenTAG NMA

	Discounted cost		Discounted QALYs		ICER
	Total	**Incremental**	**Total**	**Incremental**	
With PenTAG NMA results					
EC-MPS	£126,133	–	7.33	–	–
MMF	£90,790	£35,343	6.30	1.03	£34,167
With PenTAG NMA results and utility values					
EC-MPS	£126,396	–	7.43	–	
MMF	£90,801	£35,595	7.22	0.22	£165,379
With PenTAG NMA results and cost inputs					
EC-MPS	£104,260	–	7.35	–	–
MMF	£77,297	£26,963	6.31	1.04	£25,863
With PenTAG NMA results and NODAT					
EC-MPS	£127,333	–	7.31	–	–
MMF	£91,986	£35,347	6.27	1.04	£34,114
With PenTAG NMA results, utility values and NODAT					
EC-MPS	£127,155	–	7.39	–	–
MMF	£91,848	£35,307	7.18	0.22	£162,931
With PenTAG NMA results, utility values and cost inputs					
EC-MPS	£104,524	–	7.45	–	–
MMF	£77,584	£26,941	7.24	0.21	£126,793
With PenTAG NMA results, cost inputs, NODAT and utility values					
EC-MPS	£108,508	–	7.39	–	–
MMF	£77,056	£31,453	7.17	0.22	£145,194
With PenTAG NMA results and NODAT and cost inputs (revised case base analysis)					
EC-MPS	£106,205	–	7.31	–	–
MMF	£77,649	£28,555	6.27	1.04	£27,327

Table 6. Analysis of EC-MPS vs MMF, using clinical inputs from the Novartis analysis

	Discounted cost		Discounted QALYs		ICER
	Total	**Incremental**	**Total**	**Incremental**	
With Novartis clinical inputs					
EC-MPS	£124,338	–	7.46	–	–
MMF	£141,669	–£17,330	6.42	1.04	Dominant
With Novartis clinical inputs and PenTAG utility values					
EC-MPS	£124,755	–	7.50	–	–
MMF	£142,094	–£17,339	6.91	0.60	Dominant
With Novartis clinical inputs and PenTAG cost inputs					
EC-MPS	£101,386	–	7.46	–	–
MMF	£136,387	–£35,001	6.42	1.05	Dominant
With Novartis clinical inputs and NODAT					
EC-MPS	£125,148	–	7.42	–	–
MMF	£141,919	–£16,771	6.37	1.05	Dominant
With Novartis clinical inputs, PenTAG utility values and NODAT					
EC-MPS	£125,084	–	7.43	–	–
MMF	£141,319	–£16,234	6.83	0.60	Dominant
With Novartis clinical inputs, PenTAG utility values and PenTAG cost inputs					
EC-MPS	£101,292	–	7.47	–	–
MMF	£136,583	–£35,291	6.88	0.59	Dominant
With Novartis clinical inputs, PenTAG cost inputs, NODAT and PenTAG utility values					
EC-MPS	£103,471	–	7.45	–	–
MMF	£136,787	–£33,315	6.84	0.61	Dominant
With Novartis clinical inputs and NODAT and PenTAG cost inputs					
EC-MPS	£102,886	–	7.41	–	–
MMF	£136,697	–£33,812	6.36	1.88	Dominant

Table 7. Analysis of EC-MPS vs MMF, using long-term graft survival rates from the PenTAG analysis

	Discounted cost		Discounted QALYs		ICER
	Total	**Incremental**	**Total**	**Incremental**	
With PenTAG long-term graft survival rates					
EC-MPS	£114,908	–	7.30	–	–
MMF	£81,533	£33,374	6.37	0.93	£36,074
With PenTAG long-term graft survival rates and utility values					
EC-MPS	£115,150	–	7.54	–	–
MMF	£81,783	£33,367	6.40	1.14	£29,254
With PenTAG long-term graft survival rates and cost inputs					
EC-MPS	£89,958	–	7.30	–	–
MMF	£65,430	£24,527	6.37	0.93	£26,302
With PenTAG long-term graft survival rates and NODAT					
EC–MPS	£115,369	–	7.29	–	–
MMF	£81,627	£33,742	6.35	0.94	£36,002

Gastrointestinal adverse event subpopulation analysis

Table 8. Model updates – GI subgroup for EC-MPS

Location of update	Change in value/formula
Sheet: "Clinical" (Probability of Acute Rejection)	Cell: "D15", Trial probability for MMF + ciclosporin + corticosteroids Previous formula: *0.240* New formula: *D14*1.6*
Sheet: "Clinical (2)" (Probability of Chronic Rejection)	Cell: "D15", Trial probability for MMF + ciclosporin + corticosteroids Previous formula: *0.092* New formula: *D14*1.6*

Table 9. Summary of GI subpopulation analysis – EC-MPS as a second-line therapy after failure of MMF due to GI-related adverse events

	ICER (original analysis)	ICER (with adjusted MMF rate)
Analysis based on Novartis inputs	Dominant	Dominant
Analysis with PenTAG one-year clinical inputs	£34,167	£12,024

Table 10. Chronic rejection rates at one year

	Novartis model	Novartis model with PenTAG inputs
EC-MPS	0.0320[a]	0.0342
MMF in original model	0.0920[b]	0.0360
Adjusted MMF	0.1506	0.0589

[a] Tedesco-Silva 2010; [b] Vitko 2004

Table 11. GI subpopulation analysis (sensitivity analysis assuming no difference in effectiveness between EC-MPS and MMF in a general renal population)

	ICER (original analysis)	ICER (with adjusted MMF rate)
Analysis based on Novartis inputs	Dominant	£22,550
Analysis with PenTAG one-year clinical inputs	£34,167	£19,640