Appendix 5: Pharmacokinetic outcomes [posted as supplied by author]

Table A: Neoral pharmacokinetic outcomes

Study, year, organ	Dose adjustments allowed (y/n)	One to one dose conversion (y/n)*	Number of patients with dose adjustments (I/G)§	Time of outcome measurement	Dose* (mg/d)		Weight normalized dose (mg/kg/d)		Trough level (C0) (ng/ml)		C2 (ng/ml)		AUC (0-4) (ng/ml)* h		AUC (0-12) (ng/ml)* h		Cmax (ng/ml)		Tmax (h)		Cmax mean ratio (90% CI)	AUC mean ratio (90% CI)
					B	G	B	G	B	G	B	G	B	G	B	G	B	G	B	G	B	G
Khatami, 2013, kidney[62]	Y	N/A	Unclear	12 months post transplant			2.8 (1.1)	2.6 (1.1)	152.8 (56.3)	176.1 (81.2)	675.59 (226.2)	725.0 (280.9)										
Vitko, 2010, kidney[57]	Y	Y	Unclear	180 days post randomization	205.64 (85.0)	208.5 (97.6)			130.48 (26.1)	138.08 (32.22)	669.13 (133.83)	669.13 (133.83)										
Qazi, 2006, kidney[47]	Y	Y	0/13¶	2 weeks post randomization					185 (98)	195 (81)												
Hibberd, 2006, kidney[38]	Unclear	Y	Unclear	Days 14 and 28											3853.4 (1377.8)	3494.6 (1319.2)	880.9 (368.2)	754.8 (301.4)	1.4 (0.6)	1.9 (0.8)	0.88 (0.8-0.97)	0.93 (0.88-0.98)
David-Neto, 2004, kidney[34]	N	Y	N/A	Day 0 and day 7					156 (81)	160 (78)	734 (229)	708 (225)			3971 (1326)	4020 (1467)	1022 (357)	999 (377)	1.3 (0.3)	1.4 (0.3)	0.977	1.012
First, 1998, kidney[58]	N	Y	N/A	One week											4377 (1579)	4120 (1508)	994 (391)	890 (332)	1.3 (0.4)	1.4 (0.6)	0.93 (0.84-1.02)	0.95 (0.86-1.05)
Stephan, 1998, kidney[52]	Y	N/A	Unclear	One month post transplant			6.55 (1.29)	6.85 (1.37)	245 (92.4)	296 (82)							1123 (256)	1055 (248)	1.81 (0.39)	1.80 (0.4)		
Kim, 1998, kidney[40]	Unclear	N/A	Unclear	Unclear when measured Total study duration 4 weeks											6528.3 (1087.6)	7274.2 (1805)	1650 (30.69)	1709.6 (24.9)	1.4 (0.4)	1.4 (0.4)		
Masri, 1996, kidney[61]	Y	Unclear	19/18	One week post randomization			3.61 (1.42)	3.79 (1.46)	165.3 (36.4)	158.1 (47.9)							795.2 (247)	638.3 (167.9)				
Fisher, 1999, liver[59]	Unclear	Y	Unclear	Unclear					143 (54)	147 (58)					3572 (1448)	3397 (957)	589 (288)	503 (146)	2.9 (1.6)	3.1 (1.2)	0.93 (0.81-1.06)	0.99 (0.89-1.09)
Leet, 2009, heart[42]	Unclear	Y	Unclear	14 days on each medication																	1.30 (1.20-1.42)Ψ	1.17 (1.11-1.23)Ψ
Toman, 2002, heart[55]	Y	Y	11 (4/7)	12 weeks after randomization					148 (34.3)	196.2 (88.5)												
Diarra, 2010, kidney[35]	Unclear	Unclear	Unclear	Pre conversion and 6 months post conversion	152.7 (50.9)	152.0 (52.2)			87.53 (47.44)	81.51 (25.72)												
Al Wakeel, 2008, kidney[32]	N	Y	N/A	Pre conversion and 14 days post conversion					117.2 (62.8)	115.6 (62.8)					3778.6 (1610.5)	3634.4 (1419.1)	970.6 (39.7)	898.4 (346.5)	1.6 (0.7)	1.5 (0.7)	0.93 (0.8573-1.0358)	0.96 (0.9256-1.0355)

Al Wakeel, 2008, kidney[31]	Y	Y	2¶	Pre conversion and 14 days post conversion					171.1 (103.3)	177.1 (117.1)	760.3 (387.2)	706.5 (275.1)										
Sayyah, 2007, kidney[49]	Y	Y	0	Pre conversion and 5 days post conversion					235.16 (144.89)	193.17 (99.58)												
Masri, 2005, kidney[44]	Unclear	Y	Unclear	14 days pre and post conversion					109.8 (14.41)	109.3 (17.26)	680.5 (0.5)	689 (6)			2856	2892	773	743			(0.93-1.01)	(0.99-1.06) Only CI reported
Perlik, 2005, kidney[46]	N	Y	N/A	C0 and C2: 2 weeks pre conversion and 3 days post conversion AUC and Cmax: pre conversion and 14 days post conversion					123	114	604	591			3039	3108	725	717			0.99 (0.93-1.05)	1.02 (0.99-1.06)
Fradette, 2005, kidney[37]	Unclear	Y	Unclear	14 days pre and post conversion											3354.67 CV% (32.3)	3243.63 CV% (42.3)	841.06 CV% (36)	807.04 CV% (43.1)			0.96 (0.886-1.061)	0.981 (0.93-1.036)
Talaulikar, 2004, kidney[54]	Unclear	Y	Unclear	Pre conversion and 2 weeks post conversion					106 (48-188)**	98 (33-200)**	660 (73-1170)**	736 (106-1096)**	1730 (861-2980)**	2180 (858-2750)**	3000 (1490-5150)**	3840 (1310-5090)**						1.01 (0.94-1.1)Ψ
Masri, 2004, kidney[43]	Unclear	Y	Unclear	C0 and C2: 7 days apart AUC and Cmax: days 14 and 28					109.8 (14.41)	109.3 (17.26)	680.5 (0.5)	689 (6)			2856	2892	773	743				
Carnahan, 2003, kidney[33]	Y	Y	Unclear for the whole group, 2 for subgroup >18 months post transplant	Pre conversion and at least 2 weeks post conversion					139	156												
Durlik, 2003, kidney[36]	Unclear	Y	Unclear	Pre conversion and 2 weeks post conversion					155 (31)	138 (30)					4421 (647)	3834 (767)						
Tsang, 2003, kidney[56]	Y	Y	0	Days 1 and 8 (Neoral) Days 21 and 28 (generic)					127 (50.1)	142.6 (49.1)	728 (220)	913.3 (359.7)	2421 (722)	2637 (846)			1007 (358)	1101.9 (425.6)	1.53 (0.72)	1.8 (0.9)	1.09 (0.97-1.2)	1.09 (0.97-1.2)
Roza, 2002, kidney[48]	Y	Y	0	C0: Pre and 2 weeks post conversion AUC, Cmax and Tmax: Days 14 and 28					198 (77)	198 (80)					5016 (1648)	5008 (1767)	1247 (405)	1246 (477)	1.5 (0.4)	1.6 (0.5)	0.981 (0.922-1.044)	0.992 (0.951-1.034)

Gaston, 1999, kidney[60]	N	Y	N/A	Pre conversion and one week post conversion											4377 (1579)	4120 (1508)	994 (391)	890 (332)	1.3 (0.4)	1.4 (0.6)	0.93 (0.84-1.02)	0.95 (0.86-1.05)
Pamugas, 2012, kidney[45]	Y	N/A	Unclear	AUC (0-4), Cmax, Tmax: 4 days post transplant Other outcomes: one month post transplant	251.7 (83.5)	275.8 (67.9)					1563.5 (621)	1455.1 (305)	3169.7 (0.356)	3663.1 (0.352)			1152.32	1451.64	2.0 (0.3)	1.87 (0.27)	0.968 (0.900-1.127) Ψ	0.988 (0.953-1.08)Ψ
Kahn, 2010, kidney, incident transplants[39]	Y	N/A	Unclear	One week post transplant	268	283			192	213												
Kahn, 2010, kidney, stable transplant[39]	Y	Y	Unclear	One month pre and post conversion	53 (4)	56 (4)			133 (7)	132 (8)												
Spasovski, 2008, kidney[51]	Y	N/A	Unclear	6 months post transplant	147.8 (29.9)	191.7 (4.1)					793.2 (139.8)	597.7 (93.4)										
Sharma, 2006, kidney[50]	Y	N/A	Unclear	3 months			5.9 (2.2)	6.2 (1.4)			1342.4 (303.4)	1306.7 (254.4)										
Kraeuter, 2013, heart[41]	Y	Y	17	8 months pre and post conversion	140.67 (39.81)	134.58 (41.61)			102.2 (39.6)	79.7 (24.9)												

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§Reported as total number of dose changes post conversion from innovator to generic or as total number in the innovator group and total number in the generic group (I/G), where I=Innovator and G=generic
¶Dose adjustments occurred after measurement of outcome
Ψmean ratio and 95% confidence interval
**median (IQR)
CV= coefficient of variation
C2= drug level 2 hours after administration
AUC= area under the curve
Cmax= maximum concentration
An empty cell indicates that the outcome was not reported

Table B: Prograf pharmacokinetic outcomes

Study, year, organ	Dose adjustments allowed (y/n)	One to one dose conversion (y/n)*	Number of patients with dose adjustments (I/G)§	Timing of outcome measurements	Dose (mg/d)*		Weight normalized dose (mg/kg/d)		Concentration: dose ratio (ng/ml)/(mg/kg/d)		Trough level (ng/ml)		AUC (0-12) (ng/ml)* h		Cmax (ng/ml)		Tmax (h)		Cmax mean ratio (90% CI)	AUC mean ratio (90% CI)	Trough level ratio (90% CI)
					I	G	I	G	I	G	I	G	I	G	I	G	I	G			
Robertsen, 2014, kidney[74]	N	Y	N/A	6 weeks post transplant and 7-10 days post conversion							6.6 (1.4)	6.6 (1.5)	115 (27)	136 (38)	19.6 (6.3)	30.2 (11.6)	1.4 (0.7)	1.1 (0.5)	1.49 (1.35-1.65)	1.17 (1.10-1.24)	0.99 (0.92-1.06)
Min, 2013, kidney[68]	Y	Y	Unclear	6 months			0.086 (0.04)	0.069 (0.03)			6.89 (2.2)	5.65 (1.6)	118.5 (34.2)	106.8 (34.7)	19.6 (7.4)	19.6 (9.5)	1.4 (0.8)	1.0 (0.5)	1.145 (1.012-1.523)	1.098 (0.93-1.38)	
Alloway, 2012, kidney[63]	N	Y	N/A	Days 14 and 28							7.0 (2.1)	7.3 (1.8)	60 (37.8)	61.8 (40.6)	9.1 (5.5)	9.6 (5.5)	1.9 (1.3)	1.5 (1.1)	1.09 (1.01-1.18)	1.02 (0.97-1.08)	
Rosenberg, 2014, kidney[69]	Y	Y	(12/8)	4 weeks pre and post conversion							4.8 (4.5-5.0)Ψ	4.9 (4.6-5.2)Ψ									
McDevitt-Potter, 2011, kidney, liver, multi-organ[72]	Y	Y	20 (5/15)‖	Dose: Pre and post conversion Level: 3 most recent levels before conversion compared to first level 4-7 days post conversion	4.4 (3.2)	4.5 (2.9)					5.8 (2.1)	5.9 (2.7)									
Heavner, 2013, kidney[66]	Y	Y	(22/22)	Median level during a hospital admission							7.4	6.2									
Marfo, 2013, kidney[67]	N	Y	N/A	90 days pre and post conversion							6.8 (2.2)	6.0 (1.6)									
Connor, 2012, kidney[64]	Unclear	N/A	Unclear	One month post transplant							9.39 (8.19-10.75)**	8.66 (7.93-9.46)**									
Spence, 2012, kidney, liver, heart[70]	Y	Unclear	36-all post conversion to generic. Except for dose, outcomes were measured prior to any dose changes.	Dose: Pre conversion compared to last observed dose post conversion (average follow up 206 days) Other outcomes: On average 32 days pre conversion and 22 days post conversion	4.98 (3.37)	4.99 (3.51)					Kidney: 6.79 (1.62) Liver: 6.5 (1.53) Heart: 6.36 (1.74)	Kidney: 6.97 (2.37) Liver: 6.98 (2.14) Heart: 6.73 (1.64)									Kidney: 1.00 (0.96-1.04) Liver: 1.05 (0.96-1.15) Heart: 1.06 (0.99-1.15)
Momper, 2011, kidney, liver[73]	Y	Y	43 (kidney and liver not presented separately)	Average pre and post conversion over 50 days			Kidney: 0.087 Liver: 0.039	Kidney: 0.091 Liver: 0.041	Kidney: 125.3 (92.7) Liver: 184.1 (123.2)	Kidney: 110.4 (79.2) Liver: 154.7 (87.8)											Kidney: (0.904-0.966 Liver: (0.869-0.957). Only CI's reported.
Yu, 2012, liver[71]	Y	N/A	Unclear	Initial dose	5.8 (4.1)	5.1 (3.3)															
Dhungel, 2012, heart[65]	Y	N/A	Unclear	Mean level over 6 months post transplant							7.9 (1.8)	8.8 (1.8)									

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§Reported as total number of dose changes post conversion from trade name to generic or as total number in the brand name group and total number in the generic group (B/G), where B=brand name and G=generic
¶Dose adjustments occurred after measurement of outcomes
Ψmean and 95% confidence interval
**median (IQR)
CV= coefficient of variation
AUC= area under the curve
Cmax= maximum concentration
An empty cell indicates that the outcome was not reported

Table C: Cellcept pharmacokinetic outcomes

Study, year, organ	Dose adjustments allowed (y/n)	One to one dose conversion (y/n)*	Number of patients with dose changes (I/G)§	Timing of outcome measurements	Pre dose 12 h MPA (µg/ml)		AUC (0-3) (µg/ml)* h		AUC (0-6) (µg/ml)* h		AUC (0-12) (µg/ml)* h		Cmax (µg/ml)		Tmax (h)		Cmax mean ratio (90% CI)	AUC mean ratio (0-6) (90% CI)	AUC mean ratio (0-12) (90% CI)
					I	G	I	G	I	G	I	G	I	G	I	G			
Sunder-Plassman, 2012, kidney[78]	Unclear	Unclear	Unclear	Study day 1, 14, 28, 70, 112	2.69 (1.7)	3.00 (2.09)			33.52 (15.13)	31.10 (15.42)	49.85 (20.83)	48.26 (21.22)	16.19 (9.95)	14.31 (8.34)	1.12 (0.75)	1.34 (1.14)	0.873 (0.787-0.968)	0.923 (0.865-0.984)	0.959 (0.899-1.023)
Abdallah, 2010, kidney[75]	Unclear	N/A	Unclear	Study days 0, 7, 30, 90 and 180			27.76	26.12											
Videla, 2007, kidney[80]	Unclear	Y	Unclear	Pre conversion and 60 days post conversion	3.36 (1.41)	3.84 (0.62)			22.69 (13.7)	24.81 (6.67)									
Danguilan, 2014, kidney[79]	N	N/A	0	Unclear			38.21	36.78					7.88	6.92	1.07	1.03			
Rutkowski, 2011, kidney[77]	Y	N/A	(11/8)¶	Unclear	7.15	6.70													
Namgoong, 2013, liver[76]	Unclear	Y	Unclear	3 months pre and post conversion	1.71 (0.88)	1.83 (0.91)													

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§Reported as total number of dose changes post conversion from innovator to generic or as total number in the innovator group and total number in the generic group (I/G), where I=innovator and G=generic
¶Dose adjustments occurred after measurement of outcomes
Ψmean and 95% confidence interval
**median (IQR)
CV= coefficient of variation
AUC= area under the curve
Cmax= maximum concentration
MPA= mycophenolic acid
An empty cell indicates that the outcome was not reported