

SYNOPSIS

Pharmacokinetic Results:

The pharmacokinetic parameters of tacrolimus in patients following multiple doses (BID) of tacrolimus alone (Profile 1) and in combination with single doses of everolimus (Profile 2) and multiple doses of everolimus (Profile 3) are presented in the following table:

Parameter	Treatment		
	Tacrolimus Alone	Tacrolimus + Everolimus SD	Tacrolimus + Everolimus SS
	Profile 1 (N = 9)	Profile 2 (N = 9)	Profile 3 (N = 6)
AUC _{0-12 h} (ng.h/mL)	95.1 [37.0]	86.9 [32.9]	85.3 [51.9]
AUC _{0-24 h} (ng.h/mL)	175 [31.1]	162 [30.9]	162 [49.3]
C _{max} (ng/mL)	15.3 [55.8]	11.9 [58.9]	11.5 [42.0]
C _{trough, 12 h} (ng/mL)	5.20 ^b [31.9]	4.87 [29.7]	4.95 [60.1]
C _{trough, 24 h} (ng/mL)	5.04 [24.5]	4.66 [28.4]	5.13 [52.3]
t _{max} ^a (h)	1.25 [0.580, 2.08]	1.92 [1.00, 6.08]	2.04 [0.580, 3.25]
CL _{ss} /F (mL/min/kg)	10.1 [73.1]	11.1 [49.4]	8.67 [64.8]

Geometric mean (CV%) data are presented

N = Number of subjects studied

SD = single dose

SS = steady state

^a Median (min, max)

^b N = 8

Parameter	Everolimus Dose		
	1 mg/day (N = 4)	2 mg/day (N = 2)	3 mg/day (N = 3)
AUC _{0-12 h} (ng.h/mL)	13.7 [42.1]	23.5	31.9 [142.2]
AUC _{0-24 h} (ng.h/mL)	30.1 [25.5]	49.0 [23.8]	72.7 [95.9]
C _{max} (ng/mL)	3.43 [108.0]	9.40	7.01 [318.2]
C _{trough, 12 h} (ng/mL)	0.617 [27.0]	0.735	1.32 [93.2]
C _{trough, 24 h} (ng/mL)	0.832 [19.7]	1.47	2.18 [82.7]
t _{max} ^a (h)	1.06 [0.580, 2.08]	0.790 [0.580, 1.00]	1.02 [0.750, 1.92]
CL _{ss} /F (mL/min/kg)	15.8 [29.7]	18.6	24.1 [178.4]
AUC _{0-12 h} (norm)	1060 [29.7]	894	691 [178.4]
AUC _{0-24 h} (norm)	2320 [23.6]	1860	1580 [122.1]
C _{max} (norm)	264 [63.1]	357	152 [412.8]
C _{trough, 12 h} (norm)	47.5 [55.0]	27.9	28.6 [113.1]
C _{trough, 24 h} (norm)	64.0 [42.6]	56.0	47.3 [105.9]

Geometric mean [CV%] data are presented

N = Number of subjects studied

(norm) = Normalised for dose and body weight (mg/kg)

^a Median (min, max)

Pharmacokinetic Conclusions:

Systemic exposure of tacrolimus, based $AUC_{0-12\text{ h}}$, $AUC_{0-24\text{ h}}$, $C_{\text{trough}, 21\text{ h}}$, $C_{\text{trough}, 24\text{ h}}$ and C_{max} was independent of the co-administration of single doses of everolimus and everolimus at steady state.

Due to the low number of subjects in this study and high inter-subject variability of everolimus exposure no conclusions can be made regarding the linearity of everolimus exposure over dose.