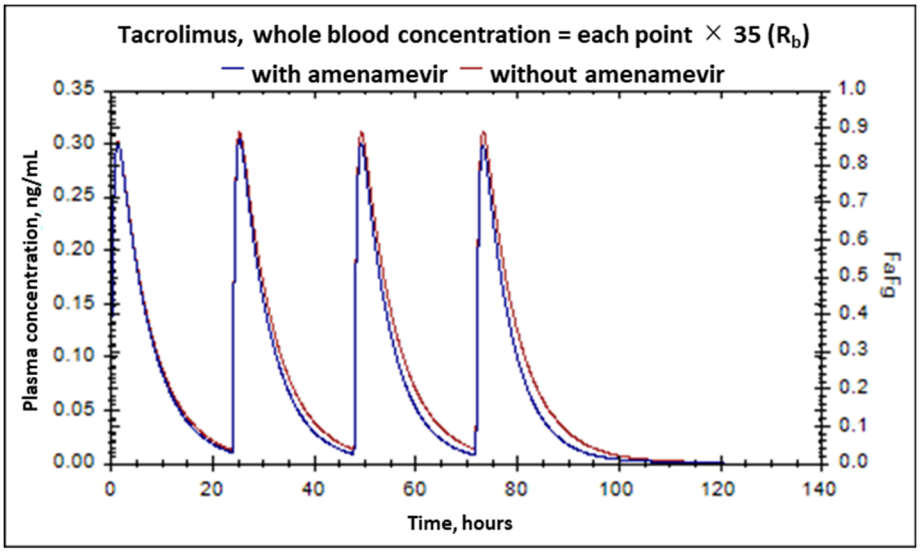
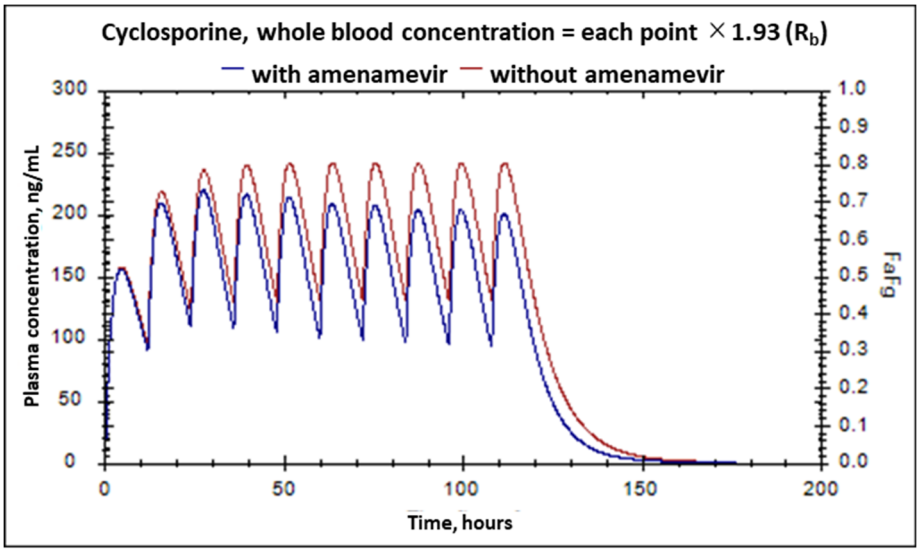
Appendix 1 Physiologically-based pharmacokinetic simulation of AUC ratio of calcineurin inhibitors co-administered amenamevir





Variables	Tacrolimus	Cyclosporine	Amenamevir
MW	804.031	572.55	482.55
LogP	3.3	3.88	2
F	0.25	0.28	0.331
F_aF_g	0.26	0.28	0.3752
F_a	0.26	0.86	0.331
k_a, 1/h	1.95	0.362	1.2275
$CL_{h,int}$, L/h	785	78.9	38.5525
CL_r, L/h	0.0379	0.20628	0.5454
V, L	19.2	22.6	92.3671
$f_{u,p}$	0.13	0.07	0.248
R_b	35	1.93	0.741
Induction of hepatic CYP3A4			
EC_{50}, μg/L			400.3
E_{max}			1.467

Abbreviations: AUC; area under the plasma drug concentration-time curve, MW; molecular weight, LogP; logarithm of octanol/water partition coefficient, F; absolute bioavailability, F_a; the fraction absorbed from the gut lumen to enterocytes, F_g; the fraction escaping first-pass gut wall metabolism, k_a; absorption rate constant, $CL_{h,int}$, intrinsic hepatic clearance, CL_r, renal clearance, V; volume distribution, $f_{u,p}$; free fraction ratio, R_b; blood-to-plasma concentration ratio, EC_{50}; 50% effective concentration, E_{max}; maximum effect

The X-axis represents the day, and the Y-axes represent the concentration of calcineurin inhibitors. Blue curve is a time-concentration curve in the presence of amenamevir. Red curve is a time-concentration curve in the absence of amenamevir. Physiologically-based pharmacokinetic simulation was operated with DDI Simulator version 2.6. (Fujitsu Limited, Tokyo, Japan) for assessing the risk of potential drug-drug interactions as a result of induction of drug metabolizing enzymes. Pharmacokinetic data of amenamevir for hepatic CYP3A4 induction was extracted from reference 3. Dosing schedules of each drug was set according to our cases.