

NONMEM code for Model 1

```
$SUBROUTINE ADVAN6 TOL=9
```

```
$MODEL
```

```
COMP=(DOSE)
```

```
COMP=(LIVER)
```

```
COMP=(CENTRAL)
```

```
COMP=(PERIPH)
```

```
COMP=(TRAN)
```

```
COMP=(TRAN)
```

```
COMP=(TRAN)
```

```
COMP=(TRAN)
```

```
COMP=(AUCPL);9
```

```
COMP=(AUCBL);10
```

```
$PK
```

```
; --- FAT FREE MASS CALCULATION -
```

```
IF (SEX.EQ.1) WHSMAX=42.92 ; MEN
```

```
IF (SEX.EQ.1) WHS50=30.93 ; MEN
```

```
IF (SEX.EQ.0) WHSMAX=37.99 ; WOMEN
```

```
IF (SEX.EQ.0) WHS50=35.98 ; WOMEN
```

```
HGT=LENG/100 ; HEIGHT CM->M
```

```
FFM=(WHSMAX*(HGT**2)*WT)/(WHS50*(HGT**2)+WT)
```

```
; --- ALLOMETRY SCALED TO 1.80M MAN OF 70 KG
```

```
ALLOCL=(FFM/57.18)**0.75
```

```
ALLOV=(FFM/57.18)
```

```
; --- LIVER VOLUME -
```

```
BSA = ((WT**0.425)*(LENG**0.725))*0.007184
```

```
POWER=1.108*(AGE**(-0.022))
```

```
VL=0.822*(BSA**POWER)
```

```
; --- FLAGS
```

```
FLA1=0
```

```
FLA2=0
```

```
FLA3=0
```

```
IF (OCC.EQ.1) FLA1=1
```

```
IF (OCC.GE.2) FLA2=1
```

```
IF (STUDY.EQ.2) FLA3=1
```

```
; --- ABSORPTION
```

```
IOVMAT=(FLA1*ETA(3))+(FLA2*ETA(4))
```

```
F1=1
```

```
MAT=THETA(1)*EXP(IOVMAT) ; CALCULATION OF MEAN ABSORPTION TIME
```

```
KA=5/MAT ; CALCULATION OF MEAN ABSORPTION TIME
```

```
; --- FLAG STUDY 4 (HIGH DOSE PREDNISOLONE)
```

```
FLA4=0
```

```
IF (STUDY.EQ.4) FLA4=1
```

```
; --- VIRTUAL AUC COMPARTMENT RESET
```

```
FLA9 = 1
```

```

IF (EVID.EQ.1) FLA9 = 0 ; ONLY INTEGRATE OVER ACTUAL DOSING INTERVAL
FLA10 = 1
IF (EVID.EQ.1) FLA10 = 0 ; ONLY INTEGRATE OVER ACTUAL DOSING INTERVAL
ENDIF

; --- DISTRIBUTION AND CLEARANCE OF EVEROLIMUS
FU=0.27*EXP(ETA(5))
QH=90*ALLOCL ; HEPATIC BLOOD FLOW L/H
QHP=QH*(1-HT) ; CALCULATE HEPATIC PLASMA FLOW
TVCLINT=THETA(2)*ALLOCL*(THETA(6)**FLA4) ; TYPICAL VALUE INTRINSIC CLEARANCE
CLINT=TVCLINT*EXP(ETA(1)) ; INTRINSIC CLEARANCE
TVV3=THETA(3)*ALLOV ; TYPICAL VALUE V3
V3=TVV3*EXP(ETA(2)) ; V3
Q=THETA(4)*ALLOCL ; INTERCOMPARTMENTAL CLEARANCE
TVV4=THETA(5)*ALLOV ; TYPICAL VALUE V4
V4=TVV4 ; V4
S3=V3 ; SCALING FOR OBSERVATIONS IN COMPARTMENT 3

; --- MASS TRANSPORT
EH=(CLINT*FU)/(QHP+(CLINT*FU)) ; HEPATIC EXTRACTION
CLH=EH*QHP ; HEPATIC CLEARANCE
K15=KA
K56=K15
K67=K56
K78=K67
K82=K78
K20=CLH/VL
K23=(QHP*(1-EH))/VL
K32=QHP/V3
K34=Q/V3
K43=Q/V4

$DES
DADT(1)=-K15*A(1)
DADT(2)=-K20*A(2)-K23*A(2)+K82*A(8)+K32*A(3)
DADT(3)=-K32*A(3)-K34*A(3)+K23*A(2)+K43*A(4)
DADT(4)=-K43*A(4)+K34*A(3)
DADT(5)=-K56*A(5)+K15*A(1)
DADT(6)=-K67*A(6)+K56*A(5)
DADT(7)=-K78*A(7)+K67*A(6)
DADT(8)=-K82*A(8)+K78*A(7)
CPLI=A(3)/V3 ; PLASMA CONCENTRATION IN V3
BMAXI=0.96425 ; DERIVED MG/L
KDI=0.09195 ; DERIVED MG/L
KNSI=0.15336 ; DERIVED MG/L
CRBI=((BMAXI*CPLI)/(KDI+CPLI))+(KNSI*CPLI) ; SPECIFIC AND NON-SPECIFIC BINDING
CBLI=(CRBI*HT)+(CPLI*(1-HT)) ; CALCULATES WHOLE BLOOD CONCENTRATIONS
DADT(9)=CPLI * FLA9 ; INTEGRATE PLASMA CONCENTRATION V3 OVER TIME
DADT(10)=CBLI * FLA10 ; INTEGRATE WHOLE BLOOD CONCENTRATION V3 OVER TIME

$ERROR
CPL=F ; CALCULATES PLASMA PK PARAMETERS IN RESULTS
BMAX=0.96425 ; DERIVED MG/L
KD=0.09195 ; DERIVED MG/L

```

KNS=0.15336 ; DERIVED MG/L
 $CRB = ((BMAX * CPL) / (KD + CPL)) + (KNS * CPL)$; SPECIFIC AND NON-SPECIFIC BINDING
 $CBL = (CRB * HT) + (CPL * (1 - HT))$; CALCULATES WHOLE BLOOD CONCENTRATIONS
 $IPRED = \log(CBL + 1E-16)$; LOG TRANSFORMED WHOLE BLOOD CONCENTRATIONS
 $Y = IPRED + ERR(1)$; RESIDUAL ERROR MODEL
 $AUCPL = A(9)$; AUC PLASMA UG/L*H
 $AUCBL = A(10)$; AUC WHOLE BLOOD UG/L*H

\$THETA
 0.458 FIX ; MEAN ABSORPTION TIME THROUGH 4 TRANSIT COMPARTMENTS (H)
 347 FIX ; INTRINSIC CLEARANCE (L/H)
 198 FIX ; V3 CENTRAL PLASMA COMPARTMENT VOLUME (L)
 86.9 FIX ; INTERCOMPARTMENTAL CLEARANCE (L/H)
 583 FIX ; V4 PERIPHERAL PLASMA COMPARTMENT VOLUME (L)
 1.28 FIX ; HIGH DOSE PRED ON CLINT

\$OMEGA
 0.114 ; IIV CLINT
 0.132 ; IIV V3
 \$OMEGA BLOCK(1) 1.06 ; IOV MAT
 \$OMEGA BLOCK(1) SAME ; IOV MAT
 \$OMEGA 0.0009 FIX ; IIV FU

\$SIGMA
 0.0313 ; PROP ERR

\$EST METHOD=1 INTER MAXEVAL=0 NOABORT NSIG=3 SIGL=9 PRINT=1 POSTHOC

NONMEM code for Model 2

\$SUBROUTINE ADVAN6 TOL=9

\$MODEL

COMP=(DOSE)

COMP=(LIVER)

COMP=(CENTRAL)

COMP=(PERIPH)

COMP=(TRAN)

COMP=(TRAN)

COMP=(TRAN)

COMP=(TRAN)

COMP=(AUCPL);9

COMP=(AUCBL);10

\$PK

VL=1.55 ; BASED ON MEAN CALCULATED LIVER VOLUME

; --- FLAGS

FLA1=0

FLA2=0

FLA3=0

IF (OCC.EQ.1) FLA1=1

IF (OCC.GE.2) FLA2=1

IF (STUDY.EQ.2) FLA3=1

; --- ABSORPTION

IOVMAT=(FLA1*ETA(3))+(FLA2*ETA(4))

F1=1

MAT=THETA(1)*EXP(IOVMAT) ; CALCULATION OF MEAN ABSORPTION TIME

KA=5/MAT ; CALCULATION OF MEAN ABSORPTION TIME

; --- FLAG STUDY 4 (HIGH DOSE PREDNISOLONE)

FLA4=0

IF (STUDY.EQ.4) FLA4=1

; --- VIRTUAL AUC COMPARTMENT RESET

FLA9 = 1

IF (EVID.EQ.1) FLA9 = 0 ; ONLY INTEGRATE OVER ACTUAL DOSING INTERVAL

FLA10 = 1

IF (EVID.EQ.1) FLA10 = 0 ; ONLY INTEGRATE OVER ACTUAL DOSING INTERVAL

; --- DISTRIBUTION AND CLEARANCE OF EVEROLIMUS

FU=0.27*EXP(ETA(5))

QH=90 ; HEPATIC BLOOD FLOW L/H

QHP=QH*(1-HT) ; CALCULATE HEPATIC PLASMA FLOW

TVCLINT=THETA(2)*(THETA(6)**FLA4) ; TYPICAL VALUE INTRINSIC CLEARANCE

CLINT=TVCLINT*EXP(ETA(1)) ; INTRINSIC CLEARANCE

TVV3=THETA(3) ; TYPICAL VALUE V3

V3=THETA(3)*EXP(ETA(2)) ; V3

Q=THETA(4) ; INTERCOMPARTMENTAL CLEARANCE

TVV4=THETA(5) ; TYPICAL VALUE V4

V4=TVV4 ; V4

S3=V3 ; SCALING FOR OBSERVATIONS IN COMPARTMENT 3

; --- MASS TRANSPORT

EH=(CLINT*FU)/(QHP+(CLINT*FU)) ; HEPATIC EXTRACTION

CLH=EH*QHP ; HEPATIC CLEARANCE

K15=KA

K56=K15

K67=K56

K78=K67

K82=K78

K20=CLH/VL

K23=(QHP*(1-EH))/VL

K32=QHP/V3

K34=Q/V3

K43=Q/V4

\$DES

DADT(1)=-K15*A(1)

DADT(2)=-K20*A(2)-K23*A(2)+K82*A(8)+K32*A(3)

DADT(3)=-K32*A(3)-K34*A(3)+K23*A(2)+K43*A(4)

DADT(4)=-K43*A(4)+K34*A(3)

DADT(5)=-K56*A(5)+K15*A(1)

DADT(6)=-K67*A(6)+K56*A(5)

DADT(7)=-K78*A(7)+K67*A(6)

DADT(8)=-K82*A(8)+K78*A(7)

CPLI=A(3)/V3 ; PLASMA CONCENTRATION IN V3

BMAXI=0.96425 ; DERIVED MG/L

KDI=0.09195 ; DERIVED MG/L

KNSI=0.15336 ; DERIVED MG/L

CRBI=((BMAXI*CPLI)/(KDI+CPLI))+(KNSI*CPLI) ; SPECIFIC AND NON-SPECIFIC BINDING

CBLI=(CRBI*HT)+(CPLI*(1-HT)) ; CALCULATES WHOLE BLOOD CONCENTRATIONS

DADT(9)=CPLI * FLA9 ; INTEGRATES PLASMA CONCENTRATION V3 OVER TIME

DADT(10)=CBLI * FLA10 ; INTEGRATES WHOLE BLOOD CONCENTRATION V3 OVER TIME

\$ERROR

CPL=F ; CALCULATES PLASMA PK PARAMETERS IN RESULTS

BMAX=0.96425 ; DERIVED MG/L

KD=0.09195 ; DERIVED MG/L

KNS=0.15336 ; DERIVED MG/L

CRB=((BMAX*CPL)/(KD+CPL))+(KNS*CPL) ; SPECIFIC AND NON-SPECIFIC BINDING

CBL=(CRB*HT)+(CPL*(1-HT)) ; CALCULATES WHOLE BLOOD CONCENTRATIONS

IPRED=LOG(CBL+1E-16) ; LOG TRANSFORMED WHOLE BLOOD CONCENTRATIONS

Y=IPRED+ERR(1) ; RESIDUAL ERROR MODEL

AUCPL=A(9) ; AUC PLASMA UG/L*H

AUCBL=A(10) ; AUC WHOLE BLOOD UG/L*H

\$THETA

0.504 FIX ; MEAN ABSORPTION TIME THROUGH 4 TRANSIT COMPARTMENTS (H)

318 FIX ; INTRINSIC CLEARANCE (L/H)

186 FIX ; V3 CENTRAL PLASMA COMPARTMENT VOLUME (L)

84.3 FIX ; INTERCOMPARTMENTAL CLEARANCE (L/H)

554 FIX ; V4 PERIPHERAL PLASMA COMPARTMENT VOLUME (L)

1.38 FIX ; HIGH DOSE PRED ON CLINT

```
$OMEGA  
0.125 ; IIV CLINT  
0.121 ; IIV V3  
$OMEGA BLOCK(1) 0.978 ; IOV MAT  
$OMEGA BLOCK(1) SAME ; IOV MAT  
$OMEGA 0.0009 FIX ; IIV FU
```

```
$SIGMA  
0.0317 ; PROP ERR
```

```
$EST METHOD=1 INTER MAXEVAL=0 NOABORT NSIG=3 SIGL=9 PRINT=1 POSTHOC
```

NONMEM code for Model 3

```
$SUBROUTINE ADVAN6 TOL=9
```

```
$MODEL
```

```
COMP=(DOSE)
```

```
COMP=(LIVER)
```

```
COMP=(CENTRAL)
```

```
COMP=(PERIPH)
```

```
COMP=(TRAN)
```

```
COMP=(TRAN)
```

```
COMP=(TRAN)
```

```
COMP=(TRAN)
```

```
COMP=(AUCPL);9
```

```
COMP=(AUCBL);10
```

```
$PK
```

```
VL=1.55 ; BASED ON MEAN CALCULATED LIVER VOLUME
```

```
; --- FLAGS
```

```
FLA1=0
```

```
FLA2=0
```

```
FLA3=0
```

```
IF (OCC.EQ.1) FLA1=1
```

```
IF (OCC.GE.2) FLA2=1
```

```
IF (STUDY.EQ.2) FLA3=1
```

```
; --- ABSORPTION
```

```
IOVMAT=(FLA1*ETA(3))+(FLA2*ETA(4))
```

```
F1=1
```

```
MAT=THETA(1)*EXP(IOVMAT) ; CALCULATION OF MEAN ABSORPTION TIME
```

```
KA=5/MAT ; CALCULATION OF MEAN ABSORPTION TIME
```

```
; --- FLAG STUDY 4 (HIGH DOSE PREDNISOLONE)
```

```
FLA4=0
```

```
IF (STUDY.EQ.4) FLA4=1
```

```
; --- VIRTUAL AUC COMPARTMENT RESET
```

```
FLA9 = 1
```

```
IF (EVID.EQ.1) FLA9 = 0 ; ONLY INTEGRATE OVER ACTUAL DOSING INTERVAL
```

```
FLA10 = 1
```

```
IF (EVID.EQ.1) FLA10 = 0 ; ONLY INTEGRATE OVER ACTUAL DOSING INTERVAL
```

```
; --- DISTRIBUTION AND CLEARANCE OF EVEROLIMUS
```

```
FU=0.27*EXP(ETA(5))
```

```
QH=90 ; HEPATIC BLOOD FLOW L/H
```

```
QHP=QH*(1-HT) ; CALCULATE HEPATIC PLASMA FLOW
```

```
TVCLINT=THETA(2)*(THETA(6)**FLA4) ; TYPICAL VALUE INTRINSIC CLEARANCE
```

```
CLINT=TVCLINT*EXP(ETA(1)) ; INTRINSIC CLEARANCE
```

```
TVV3=THETA(3) ; TYPICAL VALUE V3
```

```
V3=THETA(3)*EXP(ETA(2)) ; V3
```

```
Q=THETA(4) ; INTERCOMPARTMENTAL CLEARANCE
```

```
TVV4=THETA(5) ; TYPICAL VALUE V4
```

```
V4=TVV4 ; V4
```

S3=V3 ; SCALING FOR OBSERVATIONS IN COMPARTMENT 3

; --- MASS TRANSPORT

EH=(CLINT*FU)/(QHP+(CLINT*FU)) ; HEPATIC EXTRACTION

CLH=EH*QHP ; HEPATIC CLEARANCE

K15=KA

K56=K15

K67=K56

K78=K67

K82=K78

K20=CLH/VL

K23=(QHP*(1-EH))/VL

K32=QHP/V3

K34=Q/V3

K43=Q/V4

\$DES

DADT(1)=-K15*A(1)

DADT(2)=-K20*A(2)-K23*A(2)+K82*A(8)+K32*A(3)

DADT(3)=-K32*A(3)-K34*A(3)+K23*A(2)+K43*A(4)

DADT(4)=-K43*A(4)+K34*A(3)

DADT(5)=-K56*A(5)+K15*A(1)

DADT(6)=-K67*A(6)+K56*A(5)

DADT(7)=-K78*A(7)+K67*A(6)

DADT(8)=-K82*A(8)+K78*A(7)

CPLI=A(3)/V3 ; PLASMA CONCENTRATION IN V3

BMAXI=0.96425 ; DERIVED MG/L

KDI=0.09195 ; DERIVED MG/L

KNSI=0.15336 ; DERIVED MG/L

CRBI=((BMAXI*CPLI)/(KDI+CPLI))+(KNSI*CPLI) ; SPECIFIC AND NON-SPECIFIC BINDING

CBLI=(CRBI*HT)+(CPLI*(1-HT)) ; CALCULATES WHOLE BLOOD CONCENTRATIONS

DADT(9)=CPLI * FLA9 ; INTEGRATES PLASMA CONCENTRATION V3 OVER TIME

DADT(10)=CBLI * FLA10 ; INTEGRATES WHOLE BLOOD CONCENTRATION V3 OVER TIME

\$ERROR

CPL=F ; CALCULATES PLASMA PK PARAMETERS IN RESULTS

BMAX=0.96425 ; DERIVED MG/L

KD=0.09195 ; DERIVED MG/L

KNS=0.15336 ; DERIVED MG/L

CRB=((BMAX*CPL)/(KD+CPL))+(KNS*CPL) ; SPECIFIC AND NON-SPECIFIC BINDING

CBL=(CRB*HT)+(CPL*(1-HT)) ; CALCULATES WHOLE BLOOD CONCENTRATIONS

IPRED=LOG(CBL+1E-16) ; LOG TRANSFORMED WHOLE BLOOD CONCENTRATIONS

Y=IPRED+ERR(1) ; RESIDUAL ERROR MODEL

AUCPL=A(9) ; AUC PLASMA UG/L*H

AUCBL=A(10) ; AUC BLOOD UG/L*H

\$THETA

0.549 FIX ; MEAN ABSORPTION TIME THROUGH 4 TRANSIT COMPARTMENTS (H)

322 FIX ; INTRINSIC CLEARANCE (L/H)

266 FIX ; V3 CENTRAL PLASMA COMPARTMENT VOLUME (L)

79.5 FIX ; INTERCOMPARTMENTAL CLEARANCE (L/H)

519 FIX ; V4 PERIPHERAL PLASMA COMPARTMENT VOLUME (L)

1.44 FIX ; HIGH DOSE PRED ON CLINT

\$OMEGA
0.118 ; IIV CLINT
0.401 ; IIV V3
\$OMEGA BLOCK(1) 0 FIX ; IOV MAT
\$OMEGA BLOCK(1) SAME ; IOV MAT
\$OMEGA 0.0009 FIX ; IIV FU - KOVARIK ET AL

\$SIGMA
0.0957 ; PROP ERR

\$EST METHOD=1 INTER MAXEVAL=0 NOABORT NSIG=3 SIGL=9 PRINT=1 POSTHOC