

\$PROBLEM IOV model
\$INPUT ID DATE TIME DV MDV AMT RATE EVID BSA
\$DATA IOVwhole.prn
\$SUBROUTINES ADVAN3 TRANS4
\$PK

OCC1=0
OCC2=0
OCC3=0
OCC4=0
OCC5=0
OCC6=0
OCC7=0
OCC8=0
OCC9=0

IF(DATE.EQ.1) OCC1=1
IF(DATE.EQ.2) OCC2=1
IF(DATE.EQ.3) OCC3=1

IF(DATE.EQ.22) OCC4=1
IF(DATE.EQ.23) OCC5=1
IF(DATE.EQ.24) OCC6=1

IF(DATE.EQ.43) OCC7=1
IF(DATE.EQ.44) OCC8=1
IF(DATE.EQ.45) OCC9=1

TVCL=THETA(1)
A=ETA(1)
B=ETA(2)*OCC1+ETA(3)*OCC2+ETA(4)*OCC3
C=ETA(5)*OCC4+ETA(6)*OCC5+ETA(7)*OCC6
D=ETA(8)*OCC7+ETA(9)*OCC8+ETA(10)*OCC9
E=ETA(11)*(OCC1+OCC2+OCC3)+ETA(12)*(OCC4+OCC5+OCC6)+ETA(13)*(OCC7+OCC8+OCC9)

CL=TVCL*EXP(A+B+C+D+E)

TVV1=THETA(2)*BSA
TVQ=THETA(3)
TVV2=THETA(4)*BSA
V1=TVV1*EXP(ETA(14))
Q=TVQ*EXP(ETA(15))
V2=TVV2*EXP(ETA(16))
S1=V1
AUC=AMT/CL

\$THETA (1,7,18) ; CL
\$THETA (1,3.4,20) ; V1
\$THETA (0.1,9.4,30) ; Q
\$THETA (0.1,4,) ; V2

\$OMEGA 0.1 ;iiv CL
\$OMEGA BLOCK(1) 0.01;IOVCL C1
\$OMEGA BLOCK(1) SAME
\$OMEGA BLOCK(1) SAME

\$OMEGA BLOCK(1) 0.1 ;IOVCL C2
\$OMEGA BLOCK(1) SAME
\$OMEGA BLOCK(1) SAME
\$OMEGA BLOCK(1) 0.1 ;IOVCL C3
\$OMEGA BLOCK(1) SAME
\$OMEGA BLOCK(1) SAME
\$OMEGA BLOCK(1) 0.1 ;IOVCL intercycle
\$OMEGA BLOCK(1) SAME
\$OMEGA BLOCK(1) SAME
\$OMEGA 0.01 ;iiv V1
\$OMEGA 0 FIXED ;iiv Q
\$OMEGA 0.05 ;iiv V2

\$ERROR
DEL=0
IF (F.EQ.0) DEL=1
W=F+DEL
Y=F+W*EPS(1)
IPRED=F
IRES=DV-IPRED
IWRES=IRES/W

\$\$SIGMA .1

\$ESTIMATION METHOD=1 INTERACTION SIGDIGITS=3 NOABORT

\$COVARIANCE PRINT=E

\$TABLE ID DATE TIME CL AUC TVCL DV V1 V2 IPRED PRED
MDV EVID ONEHEADER NOPRINT FILE=IOVwholedataPARAM.PAR
\$TABLE ID TIME IPRED IWRES NOPRINT ONEHEADER FILE=sdtab1
\$TABLE ID CL V1 Q V2 ETA(1) ETA(2) ETA(3) ETA(4) ETA(5)
ETA(6) ETA(7) NOPRINT ONEHEADER FILE=pattab1