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$PROBLEM      combined model
$INPUT        ID SID STUDY DGRP AMT1 AMT2=AMT RATE1 RATE2=RATE CMT EVID
              DVID TIME DV NMDV MDV OMIT LLOQ TYPE WT FLUID INFL INFR PEXP
$DATA         dataset.csv
              IGNORE=@
              IGNORE=(DVID.GE.3,OMIT.EQ.1)

$SUBROUTINE   ADVAN6 TOL6
$MODEL        COMP=(ETX DEFDOSE DEFOBS) ; EU/L
              COMP=(DUMMY)
              COMP=(TNFA) ; ng/L
              COMP=(1EC50)
              COMP=(2EC50)
              COMP=(3EC50)
              COMP=(IL6TR1)
              COMP=(IL6TR2)
              COMP=(IL6TR3)
              COMP=(IL6)
              COMP=(IL6TR4)

$MIX
NSPOP = 2
P(1) = 1 - THETA(7)
P(2) = THETA(7)

$PK
; --- ENDOTOXIN
MU_1 = LOG(THETA(1))
MU_2 = LOG(THETA(2))
MU_3 = LOG(THETA(3))

TVEBASE = THETA(4)
IF (STUDY == 6) TVEBASE = THETA(5)
MU_4 = LOG(TVEBASE)

MU_5 = LOG(THETA(6))

VMAX = EXP(MU_1 + ETA(1))
KM = EXP(MU_2 + ETA(2))
V1 = EXP(MU_3 + ETA(3))
EBASE = EXP(MU_4 + ETA(4))
PROP = EXP(MU_5 + ETA(5))

SOIL = 0
IF (MIXNUM == 2) SOIL = EBASE * PROP

; --- TNFA
MU_6 = LOG(THETA(8))

TVS0_TNF = THETA(9)
IF (STUDY == 3 .OR. STUDY == 6) TVS0_TNF = THETA(10)
IF (STUDY == 4) TVS0_TNF = THETA(11)
IF (STUDY == 5) TVS0_TNF = THETA(12)
MU_7 = LOG(TVS0_TNF)

MU_8 = LOG(THETA(13))
MU_9 = LOG(THETA(14))
MU_10 = LOG(THETA(15))
MU_11 = LOG(THETA(16))
MU_12 = LOG(THETA(17))
MU_13 = LOG(THETA(18))

MTT_TNF = EXP(MU_6 + ETA(6))

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S0_TNF = EXP(MU_7 + ETA(7))
EMAX_TNF = EXP(MU_8 + ETA(8))
EC0_TNF = EXP(MU_9 + ETA(9))
ECMTT_TNF = EXP(MU_10 + ETA(10))
TMAX_TNF = EXP(MU_11 + ETA(11))
EGAM_TNF = EXP(MU_12 + ETA(12))
TC50_TNF = EXP(MU_13 + ETA(13))

KOUT_TNF = 1 / MTT_TNF
KIN_TNF = S0_TNF * KOUT_TNF
ECKOUT_TNF = 3 / ECMTT_TNF
ECKIN_TNF = EC0_TNF * ECKOUT_TNF

; --- IL6
MU_14 = LOG(THETA(19))

TVS0_IL6 = THETA(20)
IF (STUDY == 3 .OR. STUDY == 4 .OR. STUDY == 6) TVS0_IL6 = THETA(21)
MU_15 = LOG(TVS0_IL6)

MU_16 = LOG(THETA(22))
MU_17 = LOG(THETA(23))

MTT_IL6 = EXP(MU_14 + ETA(14))
S0_IL6 = EXP(MU_15 + ETA(15))
D1SLP_IL6 = EXP(MU_16 + ETA(16))
D2SLP_IL6 = EXP(MU_17 + ETA(17))

KOUT_IL6 = 5 / MTT_IL6
KIN_IL6 = S0_IL6 * KOUT_IL6

A_0(1) = SOIL
A_0(2) = 0
A_0(3) = S0_TNF
A_0(4) = EC0_TNF
A_0(5) = EC0_TNF
A_0(6) = EC0_TNF
A_0(7) = S0_IL6
A_0(8) = S0_IL6
A_0(9) = S0_IL6
A_0(10) = S0_IL6
A_0(11) = S0_IL6

$DES
CP = A(2) / V1
EC50 = A(6)
TOL_TNF = TMAX_TNF * CP / (TC50_TNF + CP)
EFF_TNF = EMAX_TNF * CP**EGAM_TNF / (EC50**EGAM_TNF + CP**EGAM_TNF)

CTNF = A(3)
EFF1_IL6 = D1SLP_IL6 * (CTNF / S0_TNF - 1)
EFF2_IL6 = D2SLP_IL6 * CP

DADT(1) = -VMAX * (A(1) / V1) / (KM + (A(1) / V1))
DADT(2) = -VMAX * (A(2) / V1) / (KM + (A(2) / V1))
DADT(3) = KIN_TNF * (1 + EFF_TNF) -KOUT_TNF * A(3)
DADT(4) = ECKIN_TNF * (1 + TOL_TNF) -ECKOUT_TNF * A(4)
DADT(5) = ECKOUT_TNF * A(4) -ECKOUT_TNF * A(5)
DADT(6) = ECKOUT_TNF * A(5) -ECKOUT_TNF * A(6)
DADT(7) = KIN_IL6 * (1 + EFF1_IL6 + EFF2_IL6) -KOUT_IL6 * A(7)
DADT(8) = KOUT_IL6 * A(7) -KOUT_IL6 * A(8)
DADT(9) = KOUT_IL6 * A(8) -KOUT_IL6 * A(9)
DADT(10) = KOUT_IL6 * A(11) -KOUT_IL6 * A(10)

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DADT(11)= KOUT_IL6 * A(9) -KOUT_IL6 * A(11)

\$ERROR

NIPRD = EBASE + A(1) / V1 ; BASE+ETX (EU/L)

IF (DVID == 1) NIPRD = A(3) ; TNFA (ng/L)

IF (DVID == 2) NIPRD = A(10) ; IL6 (ng/L)

IPRED = LOG(NIPRD)

IRES = DV - IPRED

W = SQRT(SIGMA(1,1))

IF (DVID == 1) W = SQRT(SIGMA(2,2))

IF (DVID == 2) W = SQRT(SIGMA(3,3))

IWRES = IRES / W

Y = IPRED + EPS(1)

IF (DVID == 2) Y = IPRED + EPS(3)

LOQ = LOG(LLOQ)

IF (TYPE.EQ.0 .AND. DVID.EQ.1) THEN

F_FLAG = 0

Y = IPRED + EPS(2)

ENDIF

IF (TYPE.EQ.1 .AND. DVID.EQ.1) THEN

DUM = (LOQ - IPRED) / W

CUMD = PHI(DUM)

F_FLAG = 1

Y = CUMD

MDVRES = 1

ENDIF

IF (TYPE.EQ.0 .AND. DVID.EQ.2) THEN

F_FLAG = 0

Y = IPRED + EPS(3)

ENDIF

IF (TYPE.EQ.1 .AND. DVID.EQ.2) THEN

DUM = (LOQ - IPRED) / W

CUMD = PHI(DUM)

F_FLAG = 1

Y = CUMD

MDVRES = 1

ENDIF

\$THETA (1E-6, 442143) ; 1 VMAX; EU/h

\$THETA (1E-6, 12325.3) ; 2 KM; EU/L

\$THETA (1E-6, 34.7795) ; 3 V1; L

\$THETA (1E-6, 157.145) ; 4 BASE; EU/L

\$THETA (1E-6, 1807.02) ; 5 BASE6; EU/L

\$THETA (1E-6, 132.529) ; 6 SCALE; -

\$THETA (0, 0.399308, 1) FIX ; 7 MIX; -

\$THETA (1E-6, 1.05168) ; 8 MTT; h

\$THETA (1E-6, 280.522) ; 9 S0; ng/L

\$THETA (1E-6, 3.00483) ; 10 S0; ng/L

\$THETA (1E-6, 66.4359) ; 11 S0; ng/L

\$THETA (1E-6, 25.2023) ; 12 S0; ng/L

\$THETA (1E-6, 2552.66) ; 13 EMAX; -

\$THETA (1E-6, 296.491) ; 14 EC0; EU/L

\$THETA (1E-6, 6.40055) ; 15 ECMTT; h

\$THETA (1E-6, 43708.4) ; 16 TMAX; -

\$THETA (1E-6, 2.11093) ; 17 EGAM; -

\$THETA (1E-6, 29802.7) ; 18 TC50; EU/L

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$THETA (1E-6, 1.42911) ; 19 MTT; h
$THETA (1E-6, 49.3472) ; 20 S0; ng/L
$THETA (1E-6, 8.03618) ; 21 S0; ng/L
$THETA (1E-6, 0.968638) ; 22 D1SLP; -
$THETA (1E-6, 0.00955112) ; 23 D2SLP; -

$OMEGA 0.000625 FIX ; 1 VMAX ETX
$OMEGA BLOCK(2)
1.44404 ; 2 KM ETX
-0.383922 0.564858 ; 3 V1 ETX
$OMEGA 0.916907 ; 4 BASE ETX
$OMEGA 0.000625 FIX ; 5 PROP ETX
$OMEGA 0.662022 ; 6 MTT TNF
$OMEGA 0.294453 ; 7 S0 TNF
$OMEGA 0.000625 FIX ; 8 EMAX TNF
$OMEGA 0.000625 FIX ; 9 EC50 TNF
$OMEGA 0.000625 FIX ; 10 TMTT TNF
$OMEGA 0.000625 FIX ; 11 TMAX TNF
$OMEGA 0.000625 FIX ; 12 EGAM TNF
$OMEGA 0.000625 FIX ; 13 TC50 TNF
$OMEGA 0.229546 ; 14 MTT IL6
$OMEGA 0.638651 ; 15 S0 IL6
$OMEGA 0.000625 FIX ; 16 D1SLP IL6
$OMEGA 0.000625 FIX ; 17 D2SLP IL6

$SIGMA 0.105128 ; 1 PropRES ETX
$SIGMA 0.235298 ; 2 PropRES TNFA
$SIGMA 0.254526 ; 3 PropRES IL6

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\$PHIS FILE=../../run045.phi

\$ESTIMATION METHOD=IMP LAPLACIAN INTERACTION MAPITER=1 MAPINTER=1 NITER=300
 AUTO=1 GRD=SN(2-3) RANMETHOD=3SP PRINT=1 POSTHOC NOABORT

MSFO=run045_msfi

\$COVARIANCE PRINT=E PRINT=R UNCONDITIONAL

\$TABLE ID SID STUDY DVID DGRP TIME CMT MDV OMIT CWRES IWRES IPRED ONEHEADER
 APPEND NOPRINT FILE=sdtab046

\$TABLE ID MTT_IL6 S0_IL6 D1SLP_IL6 D2SLP_IL6 ETAS(1:LAST) ONEHEADER NOAPPEND
 NOPRINT FILE=patab046

;\$TABLE ID WT ABSD ONEHEADER NOAPPEND NOPRINT FILE=cotab001

;\$TABLE ID STUDY INFL FLUID ONEHEADER NOAPPEND NOPRINT FILE=catab001