

```

; Timestamp: 100826-053155

; Project folder: NORMAL.NONMEM.EXECUTION
; Working folder: WORKING
; Control stream: Analyze-2CompartmentWithCovariate.pltc

; Analysis performed on TwiceTwo-2 by user fisher
; PLT Tools started at 2010-08-26 05:31:55
; NONMEM started at 2010-08-26 05:31:59
; NONMEM completed at 2010-08-26 05:33:25

;-----
; PLT Tools copied and/or reformatted the $DATA record of the control stream. The following line was replaced:
; $DATA ../DATAFILES/TwoCompartmentData.csv IGNORE=@ WIDE; "Requests that FDATA contain single-line records"
; with:
; $DATA Data.100826-053155-TEMPCOPY.txt IGNORE=@ WIDE; "Requests that FDATA contain single-line records"
;-----
;C Data for this analysis were generated with a two-compartment model in which relative bioavailability varied
;C with dose. The control stream includes a factor for F as a function of dose.
;
$PROBLEM Analyze a Dataset for Use in PLT Tools - Covariate Added
$INPUT PTID=ID          EVD1=EVID      EVD2      AMT          NTME          TIME
        DSGR           LGDS          GRUP      AGE           WT            CRCL
        CP=DV
;-----
; UNITS
; Time - hours
; Dose - mcg
; Cp - ng/ml = mcg/L
; Clearances - L/hour
; Volumes - L
;-----
; EVD1: uses all DV values
; EVD2: =2 for BQL values
; NTME: nominal time (for use in VPC graphics)
; Note aliasing of ID to PTID - Excel may fail if cell A1 starts with "ID"
$DATA Data.100826-053155-TEMPCOPY.txt IGNORE=@ WIDE; "Requests that FDATA contain single-line records"
$SUBROUTINES ADVAN4
$PK      FFCTR = 1 + (LGDS - 1.5) * THETA(8)
        CL    = THETA(1) * EXP(ETA(1))
        V1    = THETA(2) * EXP(ETA(2))
        CLRA  = THETA(3) * EXP(ETA(3))
        V2    = THETA(4) * EXP(ETA(4))
        KA    = THETA(5) * EXP(ETA(5))
        LAG   = THETA(6) * EXP(ETA(6))
        F1    = THETA(7) * EXP(ETA(7)) * FFCTR
;-----
        S1    = V1
        K     = CL / V1
        K23   = CLRA / V1
        K32   = CLRA / V2
        ALAG1 = LAG
$ERROR   IPRED = F
        Y     = IPRED * (1+EPS(1)) + EPS(2)
$THETA   (0 0.3          ) ; THETA(1) is CL
        (0 2           ) ; THETA(2) is V1

```

```

(0 0.1      ) ; THETA(3) is CLdist
(0 2        ) ; THETA(4) is V2
(0 0.5      ) ; THETA(5) is ka
(0 0.1      ) ; THETA(6) is LAG
(1 FIX     ) ; THETA(7) is F1
(0.01      ) ; THETA(8) is factor for effect of dose on F
$OMEGA (0.1  ) ; OMEGA1 applies to CL
(0.1       ) ; OMEGA2 applies to V1
(0.1       ) ; OMEGA3 applies to CLdist
(0.1       ) ; OMEGA4 applies to V2
$OMEGA (0.1  ) ; OMEGA5 applies to KA
(0.2       ) ; OMEGA6 applies to LAG
(0 FIX     ) ; OMEGA7 applies to F1
$SIGMA (0.10 ) ; SIGMA1 is proportional error term
(0.10     ) ; SIGMA2 is additive error term
$ESTIMATION
METHOD=1      PRINT=1      MAXEVALS=9999  NOABORT
SIGDIGITS=3   POSTHOC     INTER         MSFO=msfo.outputfile
$COVARIANCE
$TABLE ID      EVID      AMT      TIME      IPRED
NOPRINT FILE=AllRecords.txt
$TABLE ID
CL      V1      CLRA     V2      KA      LAG
ETA1    ETA2    ETA3     ETA4    ETA5    ETA6
FIRSTONLY  NOPRINT  NOAPPEND      FILE=FirstRecords.txt
SUMMARY OF FILE NMOUTPLTTools
PROBLEM NO.: 1
Analyze a Dataset for Use in PLT Tools - Covariate Added
INITIAL ESTIMATE OF THETA:
3.00E-01  2.00E+00  1.00E-01  2.00E+00  5.00E-01  1.00E-01  1.00E+00  1.00E-02
LOWER BOUND ON THETA:
0.00E+00  0.00E+00  0.00E+00  0.00E+00  0.00E+00  0.00E+00  1.00E+00 -1.00E+06
UPPER BOUND ON THETA:
1.00E+06  1.00E+06  1.00E+06  1.00E+06  1.00E+06  1.00E+06  1.00E+00  1.00E+06
INITIAL ESTIMATE OF OMEGA:
1.00E-01
1.00E-01
1.00E-01
1.00E-01
1.00E-01
2.00E-01
0.00E+00
INITIAL ESTIMATE OF SIGMA:
1.00E-01
0.00E+00  1.00E-01
INITIAL GRADIENT:
-2.06E+01  4.18E+01 -3.74E+01  1.70E+01  1.88E+02 -2.87E+01  1.63E+01  1.89E+01  2.46E+00 -1.65E-01  4.88E+00
-9.72E+01  1.40E+01 -1.50E+02  5.21E+01
MINIMIZATION SUCCESSFUL
HOWEVER, PROBLEMS OCCURRED WITH THE MINIMIZATION.
REGARD THE RESULTS OF THE ESTIMATION STEP CAREFULLY, AND ACCEPT THEM ONLY
AFTER CHECKING THAT THE COVARIANCE STEP PRODUCES REASONABLE OUTPUT.
NO. OF FUNCTION EVALUATIONS USED: 2030
NO. OF SIG. DIGITS IN FINAL EST.: 3.2
PARAMETER ESTIMATE IS NEAR ITS BOUNDARY
THIS MUST BE ADDRESSED BEFORE THE COVARIANCE STEP CAN BE IMPLEMENTED

```

ETABAR IS THE ARITHMETIC MEAN OF THE ETA-ESTIMATES,
 AND THE P-VALUE IS GIVEN FOR THE NULL HYPOTHESIS THAT THE TRUE MEAN IS 0.
 ETABAR

1.61E-03 1.49E-03 1.20E-07 -1.41E-06 1.69E-02 5.52E-02 0.00E+00

SE

3.62E-02 9.41E-03 2.66E-06 4.38E-06 3.54E-02 3.50E-02 0.00E+00

P VAL

9.64E-01 8.74E-01 9.64E-01 7.48E-01 6.34E-01 1.15E-01 1.00E+00

#TERE:

FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION

#OBJT:***** MINIMUM VALUE OF OBJECTIVE FUNCTION

#OBJV:***** 879.564

FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION

FINAL PARAMETER ESTIMATE

THETA - VECTOR OF FIXED EFFECTS PARAMETERS

1.50E-01 9.20E-01 6.52E-02 6.96E-01 4.61E-01 3.27E-01 1.00E+00 -7.42E-01

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS

5.95E-02

0.00E+00 1.46E-02

0.00E+00 0.00E+00 1.00E-05

0.00E+00 0.00E+00 0.00E+00 1.00E-05

0.00E+00 0.00E+00 0.00E+00 0.00E+00 7.33E-02

0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 5.85E-02

0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00

SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS

1.02E-01

0.00E+00 2.07E-03