

```
1 $PROBLEM ONE COMPARTMENT ORAL MIXED ORDER ABSORPTION ;DATE = 6/2/04 PROGRAMMER=XXXX
2 ;Dose = 100mg or 250mg
3 ;Units: Time=hr,
4 ;Concentration=ug/ml
5 ;CL/F = L/hr ; V/F = L
6
7 $DATA KAKOEST_PAR.CSV IGNORE=C
8
9 $INPUT ID TIME CONC=DV AMT CMT RATE MDV
10 ;RATE = -2 in the data file means that the duration for zero order input
11 ;will be mentioned in the controlstream and hence NONMEM calculates the RATE
12
13 $SUBROUTINE ADVAN2 TRANS2
14
15 $PK
16 CL      = THETA(1)*EXP(ETA(1))      ;CL/F
17 V       = THETA(2)*EXP(ETA(2))      ;V/F
18 KA      = THETA(3)*EXP(ETA(3))      ;Absorption rate constant
19 D2      = THETA(4)*EXP(ETA(4))      ;Duration of zero order input
20 ALAG2   = THETA(5)*EXP(ETA(5))      ;Lag time after which zero order absorption starts
21 F1      = THETA(6)*EXP(ETA(6))      ;Fraction of dose absorbed by first order process
22
23 S2 = V                                ;Scaling factor
24
25
26 $ERROR
27 IPRED=F
28 Y=F+F*ERR(1)+ERR(2)
29                                     ;Additive and proportional residual error model
30
31 $THETA (0.01,1)          ;POPCL/F
32 $THETA (0.1,10)          ;POPV/F
33 $THETA (0.1,3)           ;POPKA
34 $THETA (0.1,1)           ;POPD2
35 $THETA (0.1,2)           ;POPALAG2
36 $THETA (0.01,0.3,1)      ;POPFka
37
38 $OMEGA 0.09               ;BSVCL/F
39 $OMEGA 0.09               ;BSVV/F
40 $OMEGA 0.09               ;BSVKA
41 $OMEGA 0.04               ;BSVD2
42 $OMEGA 0.04               ;BSVALAG2
43 $OMEGA 0.04               ;BSVFka
44
45 $SIGMA 0.0025             ;ERRCV
46 $SIGMA 1                  ;ERRADD
47
48
49 $ESTIMATION METHOD=0 MAXEVAL=9999 PRINT=5 POSTHOC
50 $COVARIANCE
51
52 $TABLE ID TIME DV IPRED
53 NOPRINT ONEHEADER FILE = KAKOEST_PAR.FIT
54
55
```