```
 1  $PROBLEM PKPD Singledose i.v bolus-Stimulatory Indirect response model
 2                                          ;DATE 6-2-04  PROGRAMMER:XXXX
 3                                          ;Dose=100mg or 250mg
 4                                          ;UNITS: Time=hour, Concentration=ug/ml
 5                                          ;kin = ng/ml/hr, kout=hr-1
 6                                          ;SC50 = ug/ml
 7
 8  $DATA iv1pkpdest_idr2.csv IGNORE=C
 9
10  $INPUT ID TIME AMT EFF=DV CMT CLI VI
11
12  $SUBROUTINE ADVAN6  TRANS1 TOL=3
13
14  $MODEL
15     COMP = CENTRAL
16     COMP = EFFECT
17
18  $PK
19     CL  = CLI                 ; Individual Clearance in L/hr
20     V   = VI                  ; Individual Volume of distribution in L
21     KIN   = THETA(1)*EXP(ETA(1)) ; Basal zero order production rate of biomarker
22     KOUT  = THETA(2)*EXP(ETA(2)) ; Basal first order rate constant for elimination
23                               ; of biomarker
24     SC50  = THETA(3)*EXP(ETA(3)) ; Concentration of drug at 50% Smax
25     SMAX  = THETA(4)*EXP(ETA(4)) ; Maximum fractional stimulation
26     S1 = V
27     S2 = 1
28     F2 = KIN/KOUT                 ;Baseline response; R0 = kin/kout
29
30
31  $DES
32     DADT(1) = -CL/V*A(1)           ;Plasma compartment
33     STIM    = SMAX*A(1)/(SC50+A(1))   ;Stimulatory function
34     DADT(2) = KIN*(1+STIM)-KOUT*A(2)  ; Response
35
36  $ERROR
37     CP  = A(1)/S1
38     IPRED = F
39     Y = F*EXP(ERR(1))
40
41
42  $THETA (1,10)               ;POPKIN
43  $THETA (0.01,0.7)           ;POPKOUT
44  $THETA (1,20)               ;POPEC50
45  $THETA (0.1,4)              ;POPSMAX
46
47  $OMEGA 0.09             ;BSVKIN
48  $OMEGA 0.09             ;BSVKOUT
49  $OMEGA 0.09             ;BSVSC50
50  $OMEGA 0.09             ;BSVSMAX
51
52  $SIGMA 0.0025           ;ERRCV
53
54
55  $ESTIMATION METHOD=0  MAXEVAL=9990 PRINT=10 POSTHOC
56  $COVARIANCE
```

```
57
58  $TABLE ID TIME DV CP IPRED
59  NOPRINT ONEHEADER FILE=IV1PKPDEST_IDR2.FIT
60
```