

```

03.03.2010
14:08
$PROB est cl, v
$DATA PK_BP22023finalclean.DATA IGNORE=#
$INPUT ID WT TIME DOST IV DV AMTT=DROP RATT=DROP CMT DUR MDV
GRP PCTF
      AMT RATE RAZ=DROP RAZC=DROP HV DOSC AGE=DROP SEX=DROP
COHO
      NDVC NDV

$SUBROUTINE ADVAN6 TOL=5
$MODEL
      NCOMP=3
      COMP=(DEPOT)
      COMP=(CENTRAL)
      COMP=(PERIPH)
$PK
"FIRST
" COMMON /PRCOMG/ IDUM1, IDUM2, IMAX, IDUM4, IDUM5
" INTEGER IDUM1, IDUM2, IMAX, IDUM4, IDUM5
" IMAX=10000000

      ;; CLWT-DEFINITION START
      CLWT=(WT/68)**THETA(7)
      ;; CLWT-DEFINITION END

      ;; CL-RELATION START
      CLCOV=CLWT
      ;; CL-RELATION END

      ;; V2WT-DEFINITION START
      V2WT=(WT/68)**THETA(8)
      ;; V2WT-DEFINITION END

      ;; V2-RELATION START
      V2COV=V2WT
      ;; V2-RELATION END

TVCL = CLCOV*(THETA(1)) ;
CL=TVCL*EXP(ETA(1))
TVV2 = V2COV*(THETA(2)) ;
V2 = TVV2*EXP(ETA(2))
TVQ=THETA(3)
Q = TVQ
TV3=THETA(4)
V3 = TV3*EXP(ETA(3))

F1=THETA(5)*EXP(ETA(4))
KA=THETA(6)*EXP(ETA(5))
VM=THETA(9)*EXP(ETA(6))
KM=THETA(10)*EXP(ETA(7))

S2 = V2/1000
K = CL/V2

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K12= Q/V2
K21= Q/V3

$DES
C2=A(2)/S2
DADT(1)=-KA*A(1)
DADT(2)=KA*A(1)-K12*A(2)+K21*A(3)-K*A(2)-C2*VM/(KM+C2)
DADT(3)=K12*A(2)-K21*A(3)

$ERR

DEL = 0
IF (F.EQ.0) DEL=1
IPRED= F
W = F + DEL
IRES = DV - IPRED
IWRES= IRES / W
Y = F+(W*EPS(1)) ; proportional error CCV

$THETA
(0,0.249) ; 1~CL
(0,3.020) ; 2~V2
(0,0.231) ; 3~Q
(0,0.691) ; 4~V3
(0,0.7) ; 5~F1
(0,0.265) ; 6~KA
$THETA 0.591 FIX ;7~CLWT1
$THETA 0.48 FIX ;8~V2WT1
$THETA (0,1.8) ;8~VM
$THETA (0,3100) ;10~KM

$OMEGA
0.29 ;1~IIV_CL
0.2 ;2~IIV_V1
0 FIX ;3~IIV_V2
0.0209 ;4~IIV_F1
0.169 ;5~IIV_KA
$OMEGA 0 FIX ;6~IIV_VM
$OMEGA 0 FIX ;7~IIV_KM

$SIGMA
0.0765 ; 1~RES

$COV
$EST SIGDIGITS=3 MAXEVALS=9999 POSTHOC NOABORT PRINT=5 METHOD=
1 INTER
$TABLE
ID TIME IPRED IWRES HV
ETA1 ETA2 ETA3 ETA4 ETA5 DOST
CL Q V2 V3 K K12 K21
ID WT PCTF GRP IV DV AMT RATE CMT DUR MDV DOST TIME DOSC
NDV NDVC
ONEHEADER NOPRINT FILE=BP22023_VMKM007.FIT

1NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) DOUBLE

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PRECISION NONMEM      VERSION VI LEVEL 1.0  
DEVELOPED AND PROGRAMMED BY STUART BEAL AND LEWIS SHEINER

PROBLEM NO.:            1  
est cl, v  
0DATA CHECKOUT RUN:            NO  
DATA SET LOCATED ON UNIT NO.:    2  
THIS UNIT TO BE REWOUND:        NO  
NO. OF DATA RECS IN DATA SET: 856  
NO. OF DATA ITEMS IN DATA SET: 19  
ID DATA ITEM IS DATA ITEM NO.: 1  
DEP VARIABLE IS DATA ITEM NO.: 6  
MDV DATA ITEM IS DATA ITEM NO.: 9  
0INDICES PASSED TO SUBROUTINE PRED:  
19 3 12 13 0 0 7 0 0  
0 0

0LABELS FOR DATA ITEMS:  
ID            WT        TIME        DOST            IV            DV            CMT            DUR  
MDV  
GRP        PCTF            AMT        RATE            HV        DOSC        COHO        NDVC  
NDV

EVID  
0(NONBLANK) LABELS FOR PRED-DEFINED ITEMS:  
CL            V2            Q            V3            K            K12            K21            IPRE

IWRE  
0FORMAT FOR DATA:  
  
(E4.0,E5.0,E12.0,E5.0,E1.0,E6.0,E1.0,E12.0,E1.0,E2.0,2E12.0/6E12.0,1F2.0)

TOT. NO. OF OBS RECS:        786  
TOT. NO. OF INDIVIDUALS:    66  
0LENGTH OF THETA: 10  
0OMEGA HAS BLOCK FORM:  
1  
0 2  
0 0 3  
0 0 0 4  
0 0 0 0 5  
0 0 0 0 0 6  
0 0 0 0 0 0 7

0SIGMA HAS SIMPLE DIAGONAL FORM WITH DIMENSION: 1

0INITIAL ESTIMATE OF THETA:  
LOWER BOUND            INITIAL EST            UPPER BOUND  
0.0000E+00            0.2490E+00            0.1000E+07  
0.0000E+00            0.3020E+01            0.1000E+07  
0.0000E+00            0.2310E+00            0.1000E+07  
0.0000E+00            0.6910E+00            0.1000E+07  
0.0000E+00            0.7000E+00            0.1000E+07  
0.0000E+00            0.2650E+00            0.1000E+07  
0.5910E+00            0.5910E+00            0.5910E+00  
0.4800E+00            0.4800E+00            0.4800E+00  
0.0000E+00            0.1800E+01            0.1000E+07  
0.0000E+00            0.3100E+04            0.1000E+07

0INITIAL ESTIMATE OF OMEGA:  
BLOCK SET NO.        BLOCK

FIXED  
 1  
 NO  
 0.2900E+00  
 2  
 NO  
 0.2000E+00  
 3  
 YES  
 0.0000E+00  
 4  
 NO  
 0.2090E-01  
 5  
 NO  
 0.1690E+00  
 6  
 YES  
 0.0000E+00  
 7  
 YES  
 0.0000E+00

0 INITIAL ESTIMATE OF SIGMA:  
 0.7650E-01

0 ESTIMATION STEP OMITTED: NO  
 CONDITIONAL ESTIMATES USED: YES  
 CENTERED ETA: NO  
 EPS-ETA INTERACTION: YES  
 LAPLACIAN OBJ. FUNC.: NO  
 NO. OF FUNCT. EVALS. ALLOWED: 9999  
 NO. OF SIG. FIGURES REQUIRED: 3  
 INTERMEDIATE PRINTOUT: YES  
 ESTIMATE OUTPUT TO MSF: NO  
 ABORT WITH PRED EXIT CODE 1: NO  
 IND. OBJ. FUNC. VALUES SORTED: NO

0 COVARIANCE STEP OMITTED: NO  
 EIGENVLS. PRINTED: NO  
 SPECIAL COMPUTATION: NO  
 COMPRESSED FORMAT: NO

0 TABLES STEP OMITTED: NO  
 NO. OF TABLES: 1

0 -- TABLE 1 --  
 PRINTED: NO  
 HEADER: YES  
 FILE TO BE FORWARDED: NO

0 USER-CHOSEN ITEMS

IN THE ORDER THEY WILL APPEAR IN THE TABLE:  

ID	TIME	IPRE	IWRE	HV	ETA1	ETA2	ETA3
ETA4	ETA5	DOST	CL	Q	V2	V3	
K	K12	K21	ID	WT	PCTF	GRP	IV
DV	AMT	RATE	CMT	DUR	MDV	DOST	
	TIME	DOSC	NDV	NDVC			

1 DOUBLE PRECISION PREDPP VERSION V LEVEL 1.0

GENERAL NONLINEAR KINETICS MODEL (ADVAN6)  
 0 MODEL SUBROUTINE USER-SUPPLIED - ID NO. 9999

0MAXIMUM NO. OF BASIC PK PARAMETERS: 7  
 0COMPARTMENT ATTRIBUTES

COMPT. NO.	FUNCTION	INITIAL	ON/OFF	DOSE	
DEFAULT	DEFAULT				
		STATUS	ALLOWED	ALLOWED	FOR
DOSE	FOR OBS.				
1	DEPOT	ON	YES	YES	
YES	NO				
2	CENTRAL	ON	YES	YES	NO
YES					
3	PERIPH	ON	YES	YES	NO
NO					
4	OUTPUT	OFF	YES	NO	NO
NO					

0NRD VALUE FROM SUBROUTINE TOL: 5

1

ADDITIONAL PK PARAMETERS - ASSIGNMENT OF ROWS IN GG

COMPT. NO.	SCALE	BIOAVAIL.	ZERO-ORDER	ZERO-ORDER
		FRACTION	RATE	DURATION
ABSORB				
LAG				
1	*	8	*	*
*				
2	9	*	*	*
*				
3	*	*	*	*
*				
4	*	-	-	-
-				

- PARAMETER IS NOT ALLOWED FOR THIS MODEL

\* PARAMETER IS NOT SUPPLIED BY PK SUBROUTINE;  
 WILL DEFAULT TO ONE IF APPLICABLE

0DATA ITEM INDICES USED BY PRED ARE:

EVENT ID DATA ITEM IS DATA ITEM NO.:	19
TIME DATA ITEM IS DATA ITEM NO.:	3
DOSE AMOUNT DATA ITEM IS DATA ITEM NO.:	12
DOSE RATE DATA ITEM IS DATA ITEM NO.:	13
COMPT. NO. DATA ITEM IS DATA ITEM NO.:	7

0PK SUBROUTINE CALLED WITH EVERY EVENT RECORD.

PK SUBROUTINE NOT CALLED AT NONEVENT (ADDITIONAL OR LAGGED)  
 DOSE TIMES.

0ERROR SUBROUTINE CALLED WITH EVERY EVENT RECORD.

0DES SUBROUTINE USES COMPACT STORAGE MODE.

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MONITORING OF SEARCH:

0ITERATION NO.: 0 OBJECTIVE VALUE: 0.15647E+05 NO.

OF FUNC. EVALS.:11

CUMULATIVE NO. OF FUNC. EVALS.: 11

PARAMETER:	0.1000E+00	0.1000E+00	0.1000E+00	0.1000E+00
0.1000E+00	0.1000E+00	0.1000E+00	0.1000E+00	0.1000E+00
0.1000E+00				

GRADIENT:	0.1000E+00	0.1000E+00	0.1000E+00	
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0.1619E+03	-0.9660E+02	0.6809E+02	-0.1782E+03	-
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0.2394E+03 -0.1650E+03  0.2710E+03 -0.1505E+03  0.2939E+02
0.6832E+02
      -0.1824E+02 -0.4740E+02 -0.4730E+01
OITERATION NO.:      5      OBJECTIVE VALUE:  0.15459E+05      NO.
OF FUNC. EVALS.:13
  CUMULATIVE NO. OF FUNC. EVALS.:      72
  PARAMETER: -0.5825E-01  0.3752E-01 -0.1613E+00  0.6920E+00
0.1331E+00  0.4001E-01 -0.1323E+00  0.3364E+00 -0.9062E+00 -
0.6118E+00
      0.2470E+00  0.3003E-01 -0.7257E-01
  GRADIENT:  0.1576E+03 -0.2381E+02 -0.9243E+02  0.1506E+03 -
0.2497E+03 -0.2930E+02 -0.6353E+02  0.5782E+02 -0.2349E+02 -
0.3463E+00
      -0.2029E+02 -0.5285E+01 -0.4061E+03
OITERATION NO.:      10     OBJECTIVE VALUE:  0.15441E+05      NO.
OF FUNC. EVALS.:12
  CUMULATIVE NO. OF FUNC. EVALS.:      132
  PARAMETER: -0.1626E+00  0.2512E+00 -0.1738E+00  0.1006E+01
0.2174E+00  0.9068E-01  0.6145E+00  0.3155E+00 -0.1289E+01 -
0.5953E+00
      0.4981E+00  0.5217E-01 -0.4788E-01
  GRADIENT:  0.1693E+03  0.1448E+02 -0.3750E+02  0.3222E+02 -
0.2349E+03 -0.6546E+02  0.7605E+02 -0.1085E+02 -0.4147E+02 -
0.1421E+02
      -0.1271E+02 -0.1061E+02 -0.3072E+03
OITERATION NO.:      15     OBJECTIVE VALUE:  0.15397E+05      NO.
OF FUNC. EVALS.:12
  CUMULATIVE NO. OF FUNC. EVALS.:      194
  PARAMETER: -0.7891E-01  0.1905E+00  0.3179E-01  0.8558E+00
0.3070E+00  0.1166E+00  0.2465E+00  0.3698E+00 -0.8391E+00 -
0.7073E+00
      0.1650E+00  0.7807E-01  0.5653E-01
  GRADIENT: -0.2304E+02 -0.2541E+01 -0.9055E+01  0.1696E+02
0.2682E+02 -0.7289E+01 -0.2098E+02  0.5859E+01 -0.1779E+01
0.5584E-02
      -0.8545E+01  0.5823E+01 -0.1566E+02
OITERATION NO.:      20     OBJECTIVE VALUE:  0.15394E+05      NO.
OF FUNC. EVALS.:12
  CUMULATIVE NO. OF FUNC. EVALS.:      254
  PARAMETER: -0.1276E+00  0.2157E+00  0.7709E-01  0.8948E+00
0.3024E+00  0.1576E+00  0.5236E+00  0.6412E+00 -0.8101E+00 -
0.6954E+00
      0.2689E+00  0.3675E-01  0.6281E-01
  GRADIENT:  0.2077E+01 -0.1168E+01  0.3216E+00 -0.1300E+01 -
0.9926E+00 -0.2671E-01  0.1235E+01 -0.5163E+00 -0.3162E+00 -
0.1772E+00
      -0.1302E+00  0.3197E-02  0.9305E+00
OITERATION NO.:      25     OBJECTIVE VALUE:  0.15394E+05      NO.
OF FUNC. EVALS.:21
  CUMULATIVE NO. OF FUNC. EVALS.:      347
  PARAMETER: -0.1726E+00  0.2270E+00  0.1372E+00  0.1000E+01
0.3221E+00  0.1539E+00  0.7470E+00  0.7734E+00 -0.7754E+00 -
0.6449E+00
      0.2557E+00  0.3616E-01  0.6356E-01
  GRADIENT:  0.7098E+01 -0.1538E+01 -0.1078E+01  0.5696E+00 -
0.3434E+01  0.1309E-02  0.2148E+01 -0.1556E+00 -0.2608E+00

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	OM34	OM35	OM36	OM37	OM44
OM45	OM46	OM47	OM55	OM56	OM57
OM66	OM67	OM77	SG11		
TH 1					
+	4.13E-04				
TH 2					
+	1.78E-03	5.48E-02			
TH 3					
+	3.05E-04	2.63E-03	9.29E-04		
TH 4					
+	-2.45E-03	-1.39E-03	-5.46E-04	9.17E-02	
TH 5					
+	5.89E-04	9.14E-03	8.47E-04	6.36E-03	3.42E-03
TH 6					
+	-6.38E-05	1.52E-03	-2.29E-05	-2.65E-03	-2.77E-04
4.95E-04					
TH 7					
+	.....	.....	.....	.....	.....
.....					
TH 8					
+	.....	.....	.....	.....	.....
.....					
TH 9					
+	-8.80E-03	6.23E-02	1.37E-03	9.28E-02	7.56E-03
2.21E-03	.....	.....	5.53E-01		
TH10					
+	6.13E+00	1.74E+02	3.05E+01	-3.81E+02	-1.66E+00
1.57E+01	.....	.....	5.25E+02	4.20E+06	
OM11					
+	-1.34E-04	-5.51E-04	-2.06E-04	-1.31E-04	-4.12E-04
7.48E-05	.....	.....	2.11E-03	-2.10E+00	2.22E-04
OM12					
+	.....	.....	.....	.....	.....
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OM13					
+	.....	.....	.....	.....	.....
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OM14					

+ .....  
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OM15

+ .....  
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OM16

+ .....  
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OM17

+ .....  
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OM22

+       -9.10E-05   6.91E-04   3.65E-05   1.10E-03   2.21E-05 -  
 1.54E-05 .....                   4.04E-03   2.60E+00   1.01E-05  
 .....  
 3.94E-04

1

	TH 1	TH 2	TH 3	TH 4	TH 5
TH 6	TH 7	TH 8	TH 9	TH10	OM11
OM12					
	OM13	OM14	OM15	OM16	OM17
OM22	OM23	OM24	OM25	OM26	OM27
OM33					
	OM34	OM35	OM36	OM37	OM44
OM45	OM46	OM47	OM55	OM56	OM57
OM66					
	OM67	OM77	SG11		

OM23

+ .....  
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OM24

+ .....  
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OM25

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OM26

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OM27

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OM33

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OM34

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OM35

+ .....  
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OM36

+ .....  
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TH 2
+      3.74E-01  1.00E+00

TH 3
+      4.93E-01  3.69E-01  1.00E+00

TH 4
+     -3.98E-01 -1.97E-02 -5.92E-02  1.00E+00

TH 5
+      4.96E-01  6.67E-01  4.75E-01  3.59E-01  1.00E+00

TH 6
+     -1.41E-01  2.91E-01 -3.37E-02 -3.93E-01 -2.13E-01
1.00E+00

TH 7
+      .....

TH 8
+      .....

TH 9
+     -5.82E-01  3.58E-01  6.05E-02  4.12E-01  1.74E-01
1.33E-01 ..... 1.00E+00

TH10
+      1.47E-01  3.63E-01  4.89E-01 -6.13E-01 -1.38E-02
3.45E-01 ..... 3.44E-01  1.00E+00

OM11
+     -4.43E-01 -1.58E-01 -4.53E-01 -2.90E-02 -4.73E-01
2.26E-01 ..... 1.91E-01 -6.87E-02  1.00E+00

OM12
+      .....

OM13
+      .....

OM14
+      .....

OM15
+      .....

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OM16  
+ .....  
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OM17  
+ .....  
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OM22  
+       -2.26E-01   1.49E-01   6.02E-02   1.83E-01   1.90E-02 -  
3.48E-02 .....       2.73E-01   6.39E-02   3.41E-02 -  
.....  
1.00E+00

1

	TH 1	TH 2	TH 3	TH 4	TH 5
TH 6	TH 7	TH 8	TH 9	TH10	OM11
OM12					
	OM13	OM14	OM15	OM16	OM17
OM22	OM23	OM24	OM25	OM26	OM27
OM33					
	OM34	OM35	OM36	OM37	OM44
OM45	OM46	OM47	OM55	OM56	OM57
OM66					
	OM67	OM77	SG11		

OM23  
+ .....  
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OM24  
+ .....  
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OM25  
+ .....  
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OM26

+ .....  
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OM27

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OM33

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OM34

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OM35

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OM36

+ .....  
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OM37

+ .....  
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TH 4
+      2.85E+02  4.11E+01 -1.45E+03  4.36E+02

TH 5
+      -4.03E+03 -1.39E+02  3.06E+01 -1.62E+02  2.06E+03

TH 6
+      6.43E+03 -4.15E+02 -2.00E+03  3.11E+02  1.37E+02
5.80E+03

TH 7
+      .....

TH 8
+      .....

TH 9
+      7.28E+02 -3.85E+01  3.91E+02 -1.31E+02 -6.33E+01
5.60E+01 ..... 6.09E+01

TH10
+      -8.07E-02  7.43E-03 -2.31E-01  6.60E-02  5.51E-03
1.55E-02 ..... -2.31E-02  1.12E-05

OM11
+      -2.06E+03 -2.20E+01 -1.01E+03  6.37E+02  1.70E+03 -
6.99E+02 ..... -3.06E+02  1.27E-01  1.04E+04

OM12
+      .....

OM13
+      .....

OM14
+      .....

OM15
+      .....

OM16
+      .....

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OM17
+ .....
.....
.....

OM22
+ 3.22E+03 -2.30E+02 4.55E+01 -2.09E+02 6.25E+01
1.02E+03 ..... 1.17E+02 -4.07E-02 -8.08E+02
.....
3.62E+03

1

      TH 1      TH 2      TH 3      TH 4      TH 5
TH 6    TH 7    TH 8    TH 9    TH10    OM11
OM12

      OM13      OM14      OM15      OM16      OM17
OM22    OM23    OM24    OM25    OM26    OM27
OM33

      OM34      OM35      OM36      OM37      OM44
OM45    OM46    OM47    OM55    OM56    OM57
OM66

      OM67      OM77      SG11

OM23
+ .....
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OM24
+ .....
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OM25
+ .....
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OM26
+ .....
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OM27

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OM33

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OM34

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OM35

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OM36

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OM37

+ .....  
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OM44

+ -3.10E+03 1.13E+02 4.89E+02 -1.79E+02 -1.40E+03 -  
3.07E+02 ..... 6.13E+01 -2.52E-02 -5.13E+03  
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1.33E+03 .....  
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 ..... 2.24E+04

OM45  
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OM46  
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OM47  
 + .....  
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	TH 1	TH 2	TH 3	TH 4	TH 5
TH 6	TH 7	TH 8	TH 9	TH10	OM11
OM12					
	OM13	OM14	OM15	OM16	OM17
OM22	OM23	OM24	OM25	OM26	OM27
OM33					
	OM34	OM35	OM36	OM37	OM44
OM45	OM46	OM47	OM55	OM56	OM57
OM66					
	OM67	OM77	SG11		

OM55  
 + 4.90E+02 -3.15E+00 -3.53E+01 9.76E+01 -1.68E+02 -  
 5.68E+02 ..... -2.66E+01 1.21E-02 3.32E+01  
 .....  
 2.33E+02 .....  
 .....  
 ..... 1.80E+02

..... 9.28E+02

OM56

+ .....  
.....  
.....  
.....  
.....  
.....  
.....

OM57

+ .....  
.....  
.....  
.....  
.....  
.....  
.....

OM66

+ .....  
.....  
.....  
.....  
.....  
.....  
.....

OM67

+ .....  
.....  
.....  
.....  
.....  
.....  
.....

OM77

+ .....  
.....  
.....  
.....  
.....  
.....  
.....

```

SG11
+      2.56E+03 -2.07E+02  2.95E+03 -1.47E+03 -3.24E+01
3.35E+03 ..... 5.07E+02 -3.02E-01 -7.03E+03
.....
.....
2.92E+03 .....
.....
..... 1.95E+03
..... 1.33E+02 .....
.....
..... 3.85E+04

```

```

Stop Time:
03.03.2010
14:11

```