SUPPLEMENTAL MATERIAL

A Drug-Disease Model Describing the Effect of Oseltamivir Neuraminidase Inhibition on Influenza Virus Progression

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Final Drug Treatment Model Output

```
$PROB TX13
; final run for drug treatment model

$INPUT  ID STUD AMT TIME DV CMT EVID DOSE NDD VNO
$DATA VT_PLAC_03.XSLX
  IGNORE=C
  IGNORE(STUD.NE.15616)
;  IGNORE(DOSE.NE.0)
  IGNORE(NDD.EQ.1)

$THETA  (-8,-3.26,0)    ;1 log10 BETA      ; TCID50/mL**-1 day**-1
$THETA  (-8,-3.43,0)    ;2 log10 PV        ; TCID50/mL     day**-1
$THETA  (0,6.56)        ;3 CV              ; day**-1
$THETA  (0,2.70)        ;4 DI              ; day**-1
$THETA  1.77 F          ;5 V0              ; TCID50/mL  log10 TCID50 = 0.25
$THETA  4 F             ;6 T0              ; # * 10^8
$THETA  1               ;7 Emax TX effect on pvL
$THETA  (0,10)          ;8 mg D50

$OMEGA  0 FIXED         ;1 BETA
$OMEGA  0.5             ;2 PV
$OMEGA  0 FIXED         ;3 CV
$OMEGA  0 FIXED         ;4 DI
$OMEGA  0 FIXED         ;5 V0
$OMEGA  0.5             ;6 INH

$SUBROUTINES  ADVAN9  TOL=9
$MODEL
  COMP=(TARGET)             ; Target cells   - #
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  COMP=(INFECTED)           ; Infected cells - #
  COMP=(VIRUS)              ; Virus         - TCID50/ml
  COMP=(DOSING)             ; Dose OP       - mg

$PK
   AA4  = A(4)
   XXA  = 0
   IF(AA4.GT.0) XXA=1

   INH  = THETA(7)+ETA(6)
   ID50 = THETA(8)
   INHT = INH*DOSE/(DOSE+ID50)*XXA

   BETA = 10**THETA(1)*EXP(ETA(1))
   PV   = 10**(THETA(2)-INHT)*EXP(ETA(2))
   CV   = THETA(3)*EXP(ETA(3))
   DI   = THETA(4)*EXP(ETA(4))
   V0   = THETA(5)*EXP(ETA(5))
   T0   = THETA(6)*10**8;
   F1   = T0
   F3   = V0

$DES
   DADT(1) = -BETA*A(1)*A(3)
   DADT(2) =  BETA*A(1)*A(3) - DI*A(2)
   DADT(3) =  PV*A(2)        - CV*A(3)
   DADT(4) =  0

$ERROR
   IPRE=LOG10(F)
```

```
  Y=IPRE+ERR(1)


$SIGMA  1.25


$EST  MAXEVAL=9999 PRINT=1 METHOD=1 NOABORT MSFO=TX12.MSF SIGL=9 NSIG=3
;$SIMULATION  (123456) ONLYSIM
$COV SIGL=10 TOL=10
$TABLE ID STUD TIME CMT EVID IPRE BETA PV CV DI V0
DOSE NDD VNO INHT AA4
NOPRINT ONEHEADER FILE=TX12.FIT
$TABLE ID STUD DOSE BETA PV CV DI V0 T0 INH FIRSTONLY
NOPRINT ONEHEADER FILE=TX12IND.PAR


NM-TRAN MESSAGES


 WARNINGS AND ERRORS (IF ANY) FOR PROBLEM    1


 (WARNING  2) NM-TRAN INFERS THAT THE DATA ARE POPULATION.


License Registered to: F. Hoffmann-La Roche AG
Expiration Date:    14 OCT 2015
Current Date:       19 MAR 2015
Days until program expires : 205
1NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) VERSION 7.3.0
 ORIGINALLY DEVELOPED BY STUART BEAL, LEWIS SHEINER, AND ALISON BOECKMANN
 CURRENT DEVELOPERS ARE ROBERT BAUER, ICON DEVELOPMENT SOLUTIONS,
 AND ALISON BOECKMANN. IMPLEMENTATION, EFFICIENCY, AND STANDARDIZATION
 PERFORMED BY NOUS INFOSYSTEMS.


 PROBLEM NO.:         1
```

TX13

0DATA CHECKOUT RUN: NO

DATA SET LOCATED ON UNIT NO.: 2

THIS UNIT TO BE REWOUND: NO

NO. OF DATA RECS IN DATA SET: 511

NO. OF DATA ITEMS IN DATA SET: 11

ID DATA ITEM IS DATA ITEM NO.: 1

DEP VARIABLE IS DATA ITEM NO.: 5

MDV DATA ITEM IS DATA ITEM NO.: 11

0INDICES PASSED TO SUBROUTINE PRED:

7 4 3 0 0 0 6 0 0 0 0

0LABELS FOR DATA ITEMS:

ID STUD AMT TIME DV CMT EVID DOSE NDD VNO MDV

0(NONBLANK) LABELS FOR PRED-DEFINED ITEMS:

AA4 INH INHT BETA PV CV DI V0 T0 IPRE

0FORMAT FOR DATA:

(10E6.0,1F2.0)

TOT. NO. OF OBS RECS: 311

TOT. NO. OF INDIVIDUALS: 53

0LENGTH OF THETA: 8

0DEFAULT THETA BOUNDARY TEST OMITTED: NO

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

0DEFAULT OMEGA BOUNDARY TEST OMITTED: NO

0SIGMA HAS SIMPLE DIAGONAL FORM WITH DIMENSION: 1

0DEFAULT SIGMA BOUNDARY TEST OMITTED: NO

0INITIAL ESTIMATE OF THETA:

LOWER BOUND	INITIAL EST	UPPER BOUND
-0.8000E+01	-0.3260E+01	0.0000E+00
-0.8000E+01	-0.3430E+01	0.0000E+00
0.0000E+00	0.6560E+01	0.1000E+07
0.0000E+00	0.2700E+01	0.1000E+07
0.1770E+01	0.1770E+01	0.1770E+01
0.4000E+01	0.4000E+01	0.4000E+01
-0.1000E+07	0.1000E+01	0.1000E+07
0.0000E+00	0.1000E+02	0.1000E+07

0INITIAL ESTIMATE OF OMEGA:

BLOCK SET NO.	BLOCK	FIXED
1		YES
	0.0000E+00	
2		NO
	0.5000E+00	
3		YES
	0.0000E+00	
4		YES
	0.0000E+00	
5		YES
	0.0000E+00	
6		NO
	0.5000E+00	

0INITIAL ESTIMATE OF SIGMA:

0.1250E+01

0COVARIANCE STEP OMITTED: NO

EIGENVLS. PRINTED: NO

SPECIAL COMPUTATION: NO

COMPRESSED FORMAT: NO

SIGDIGITS ETAHAT (SIGLO): -1

SIGDIGITS GRADIENTS (SIGL): 10

RELATIVE TOLERANCE (TOL): 10

ABSOLUTE TOLERANCE-ADVAN 9,13 ONLY (ATOL): -1

EXCLUDE COV FOR FOCE (NOFCOV): NO

RESUME COV ANALYSIS (RESUME): NO

0TABLES STEP OMITTED: NO

NO. OF TABLES: 2

SEED NUMBER (SEED): 11456

RANMETHOD:

MC SAMPLES (ESEED): 300

WRES SQUARE ROOT TYPE: EIGENVALUE

0-- TABLE 1 --

PRINTED: NO

HEADER: YES

FILE TO BE FORWARDED: NO

FORMAT: S1PE11.4

LFORMAT:

RFORMAT:

0USER-CHOSEN ITEMS:

ID STUD TIME CMT EVID IPRE BETA PV CV DI V0 DOSE NDD VNO INHT AA4

0-- TABLE 2 --

0FIRST RECORDS ONLY: YES

PRINTED: NO

HEADER: YES

FILE TO BE FORWARDED: NO

FORMAT: S1PE11.4

LFORMAT:

RFORMAT:

0USER-CHOSEN ITEMS:

ID STUD DOSE BETA PV CV DI V0 T0 INH

1DOUBLE PRECISION PREDPP VERSION 7.3.0

GENERAL NONLINEAR KINETICS MODEL WITH EQUILIBRIUM COMPARTMENTS (ADVAN9)

0MODEL SUBROUTINE USER-SUPPLIED - ID NO. 9999

0MAXIMUM NO. OF BASIC PK PARAMETERS: 4

0COMPARTMENT ATTRIBUTES

COMPT. NO.	FUNCTION	INITIAL STATUS	ON/OFF ALLOWED	DOSE ALLOWED	DEFAULT FOR DOSE	DEFAULT FOR OBS.
1	TARGET	ON	YES	YES	YES	YES
2	INFECTED	ON	YES	YES	NO	NO
3	VIRUS	ON	YES	YES	NO	NO
4	DOSING	ON	YES	YES	NO	NO
5	OUTPUT	OFF	YES	NO	NO	NO

0

COMPT. NO.	FUNCTION	EQUILIBRIUM	EXCLUDE FROM TOTAL
1	TARGET	NO	NO
2	INFECTED	NO	NO
3	VIRUS	NO	NO
4	DOSING	NO	NO
5	OUTPUT	NO	YES

0NRD VALUE(S) FROM SUBROUTINE TOL: 9

1

ADDITIONAL PK PARAMETERS - ASSIGNMENT OF ROWS IN GG

COMPT. NO.	INDICES			
	SCALE	BIOAVAIL. FRACTION	ZERO-ORDER RATE	ZERO-ORDER DURATION	ABSORB LAG
1	*	5	*	*	*

```
 2        *        *        *        *        *
 3        *        6        *        *        *
 4        *        *        *        *        *
 5        *        -        -        -        -
          - 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.:      7
  TIME DATA ITEM IS DATA ITEM NO.:          4
  DOSE AMOUNT DATA ITEM IS DATA ITEM NO.:   3
  COMPT. NO. DATA ITEM IS DATA ITEM NO.:    6

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 FULL STORAGE MODE.
1



 #TBLN:      1
 #METH: First Order Conditional Estimation

 ESTIMATION STEP OMITTED:                NO
 ANALYSIS TYPE:                          POPULATION
 CONDITIONAL ESTIMATES USED:             YES
 CENTERED ETA:                           NO
 EPS-ETA INTERACTION:                    NO
 LAPLACIAN OBJ. FUNC.:                   NO
 NO. OF FUNCT. EVALS. ALLOWED:           9999
```

NO. OF SIG. FIGURES REQUIRED: 3

INTERMEDIATE PRINTOUT: YES

ESTIMATE OUTPUT TO MSF: YES

ABORT WITH PRED EXIT CODE 1: NO

IND. OBJ. FUNC. VALUES SORTED: NO

NUMERICAL DERIVATIVE

FILE REQUEST (NUMDER): NONE

MAP (ETAHAT) ESTIMATION METHOD (OPTMAP): 0

ETA HESSIAN EVALUATION METHOD (ETADER): 0

INITIAL ETA FOR MAP ESTIMATION (MCETA): 0

SIGDIGITS FOR MAP ESTIMATION (SIGLO): 9

GRADIENT SIGDIGITS OF

FIXED EFFECTS PARAMETERS (SIGL): 9

EXCLUDE TITLE (NOTITLE): NO

EXCLUDE COLUMN LABELS (NOLABEL): NO

NOPRIOR SETTING (NOPRIOR): OFF

NOCOV SETTING (NOCOV): OFF

DERCONT SETTING (DERCONT): OFF

ABSOLUTE TOLERANCE-ADVAN 9,13 ONLY(ATOL):-100

FINAL ETA RE-EVALUATION (FNLETA): ON

EXCLUDE NON-INFLUENTIAL (NON-INFL.) ETAS

IN SHRINKAGE (ETASTYPE): NO

NON-INFL. ETA CORRECTION (NONINFETA): OFF

FORMAT FOR ADDITIONAL FILES (FORMAT): S1PE12.5

PARAMETER ORDER FOR OUTPUTS (ORDER): TSOL

ADDITIONAL CONVERGENCE TEST (CTYPE=4)?: NO

EM OR BAYESIAN METHOD USED: NONE

THE FOLLOWING LABELS ARE EQUIVALENT

PRED=NPRED

RES=NRES

WRES=NWRES

IWRS=NIWRES

IPRD=NIPRED

IRS=NIRES

MONITORING OF SEARCH:

0ITERATION NO.: 0 OBJECTIVE VALUE: 494.406288067358 NO. OF FUNC. EVALS.: 9

CUMULATIVE NO. OF FUNC. EVALS.: 9

NPARAMETR: -3.2600E+00 -3.4300E+00 6.5600E+00 2.7000E+00 1.0000E+00 1.0000E+01 5.0000E-01 5.0000E-01 1.2500E+00

PARAMETER: 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01

GRADIENT: -8.7219E+01 -7.7344E+01 3.7690E+01 2.6814E+01 -2.4457E+02 -9.1332E-01 2.0024E+01 1.8397E+01 3.5609E+01

0ITERATION NO.: 1 OBJECTIVE VALUE: 487.541046509050 NO. OF FUNC. EVALS.: 11

CUMULATIVE NO. OF FUNC. EVALS.: 20

NPARAMETR: -3.2341E+00 -3.4067E+00 6.5220E+00 2.6889E+00 1.3769E+00 1.0001E+01 4.9692E-01 4.9717E-01 1.2364E+00

PARAMETER: 1.1344E-01 1.1192E-01 9.4192E-02 9.5868E-02 1.3769E-01 1.0014E-01 9.6914E-02 9.7165E-02 9.4512E-02

GRADIENT: 1.9141E+01 -1.4367E+01 4.7295E+01 4.8227E+01 -2.3818E+01 -3.8153E+00 2.3720E+01 1.9679E+01 2.9829E+01

0ITERATION NO.: 2 OBJECTIVE VALUE: 478.726500851509 NO. OF FUNC. EVALS.: 10

CUMULATIVE NO. OF FUNC. EVALS.: 30

NPARAMETR: -3.3678E+00 -3.3396E+00 5.6720E+00 2.3287E+00 1.8055E+00 1.0117E+01 4.3209E-01 4.4292E-01 1.0397E+00

PARAMETER: 4.4455E-02 1.4632E-01 -4.5443E-02 -4.7934E-02 1.8055E-01 1.1166E-01 2.7018E-02 3.9393E-02 7.8852E-03

GRADIENT: -1.1325E+02 -7.0783E+01 4.9786E+01 -2.1242E+01 5.0184E+01 -3.8604E+00 1.0595E+01 6.8018E+00 -5.0970E+01

0ITERATION NO.: 3 OBJECTIVE VALUE: 477.581537215449 NO. OF FUNC. EVALS.: 11

CUMULATIVE NO. OF FUNC. EVALS.: 41

NPARAMETR: -3.3588E+00 -3.3157E+00 5.5429E+00 2.2943E+00 1.7740E+00 1.0136E+01 4.2375E-01 4.3607E-01 1.0312E+00

PARAMETER: 4.9089E-02 1.5857E-01 -6.8468E-02 -6.2820E-02 1.7740E-01 1.1355E-01 1.7269E-02 3.1593E-02 3.8019E-03

GRADIENT: -2.8116E+01 2.1577E+01 2.9576E+01 -3.3867E+01 -4.7189E+00 -2.4826E+00 8.9120E+00 7.1164E+00 -5.6918E+01

0ITERATION NO.: 4 OBJECTIVE VALUE: 473.131679800468 NO. OF FUNC. EVALS.: 11

CUMULATIVE NO. OF FUNC. EVALS.: 52

NPARAMETR: -3.3518E+00 -3.3550E+00 4.9624E+00 2.2542E+00 1.9028E+00 1.0231E+01 3.8620E-01 4.0427E-01 1.1297E+00

PARAMETER: 5.2656E-02 1.3840E-01 -1.7910E-01 -8.0477E-02 1.9028E-01 1.2288E-01 -2.9129E-02 -6.2604E-03 4.9425E-02

GRADIENT: -3.8424E+01 1.7909E+01 1.9015E+01 -3.8820E+01 1.5692E+01 -2.3365E+00 1.4601E+00 3.3927E+00 -9.4501E+00

0ITERATION NO.: 5 OBJECTIVE VALUE: 469.404624960081 NO. OF FUNC. EVALS.: 10

CUMULATIVE NO. OF FUNC. EVALS.: 62

NPARAMETR: -3.2868E+00 -3.4589E+00 4.4459E+00 2.3100E+00 1.9197E+00 1.0346E+01 3.5802E-01 3.7501E-01 1.0678E+00

PARAMETER: 8.6150E-02 8.5282E-02 -2.8901E-01 -5.6005E-02 1.9197E-01 1.3399E-01 -6.7005E-02 -4.3823E-02 2.1237E-02

GRADIENT: -3.5803E+01 1.6678E+00 1.3276E+01 -2.9336E+01 1.6625E+01 -2.0945E+00 -6.7975E+00 7.7143E-01 -3.6546E+01

0ITERATION NO.: 6 OBJECTIVE VALUE: 468.688607727220 NO. OF FUNC. EVALS.: 10

CUMULATIVE NO. OF FUNC. EVALS.: 72

NPARAMETR: -3.2756E+00 -3.4929E+00 4.1431E+00 2.3029E+00 1.9615E+00 1.0565E+01 4.3773E-01 3.5555E-01 1.0598E+00

PARAMETER: 9.1907E-02 6.7947E-02 -3.5956E-01 -5.9084E-02 1.9615E-01 1.5497E-01 3.3503E-02 -7.0465E-02 1.7466E-02

GRADIENT: -4.5414E+01 -1.6730E+00 7.9760E+00 -3.0216E+01 2.0867E+01 -1.9588E+00 6.2959E+00 -2.0206E+00 -3.9954E+01

0ITERATION NO.: 7 OBJECTIVE VALUE: 468.593116746580 NO. OF FUNC. EVALS.: 10

CUMULATIVE NO. OF FUNC. EVALS.: 82

NPARAMETR: -3.1341E+00 -3.6526E+00 4.1687E+00 2.1076E+00 1.9278E+00 1.1481E+01 4.6692E-01 3.5545E-01 1.0820E+00

PARAMETER: 1.6562E-01 -1.2821E-02 -3.5340E-01 -1.4771E-01 1.9278E-01 2.3812E-01 6.5774E-02 -7.0619E-02 2.7826E-02

GRADIENT: -4.5420E+01 -1.7008E+01 1.1553E+01 -3.3905E+01 1.1590E+01 -1.7895E+00 6.4877E+00 -1.9409E+00 -3.4170E+01

0ITERATION NO.: 8 OBJECTIVE VALUE: 466.322445761077 NO. OF FUNC. EVALS.: 11

CUMULATIVE NO. OF FUNC. EVALS.: 93

NPARAMETR: -3.1465E+00 -3.6606E+00 3.9182E+00 2.2391E+00 2.0239E+00 2.2356E+01 4.5058E-01 4.3766E-01 1.0997E+00

PARAMETER: 1.5912E-01 -1.6827E-02 -4.1535E-01 -8.7183E-02 2.0239E-01 9.0452E-01 4.7962E-02 3.3412E-02 3.5957E-02

GRADIENT: -5.2699E+01 -2.0016E+01 6.9085E-01 -2.7130E+01 -6.3824E+01 3.0741E+00 2.6996E+00 7.8606E-01 -2.3125E+01

0ITERATION NO.: 9 OBJECTIVE VALUE: 465.772631256002 NO. OF FUNC. EVALS.: 10

CUMULATIVE NO. OF FUNC. EVALS.: 103

NPARAMETR: -3.1509E+00 -3.6307E+00 4.0973E+00 2.3504E+00 1.9584E+00 2.2649E+01 4.3425E-01 2.9309E-01 1.1198E+00

PARAMETER: 1.5677E-01 -1.7957E-03 -3.7066E-01 -3.8647E-02 1.9584E-01 9.1752E-01 2.9507E-02 -1.6706E-01 4.5014E-02

GRADIENT: -1.1342E+01 1.0763E-01 4.7626E+00 -1.0796E+01 -2.8839E+01 2.3777E+00 3.5053E+00 -2.7686E+00 -1.3550E+01

0ITERATION NO.: 10 OBJECTIVE VALUE: 464.456273705012 NO. OF FUNC. EVALS.: 11

CUMULATIVE NO. OF FUNC. EVALS.: 114

NPARAMETR: -3.1459E+00 -3.6603E+00 3.7046E+00 2.4268E+00 1.9846E+00 1.6271E+01
4.2098E-01 3.7702E-01 1.1328E+00

PARAMETER: 1.5939E-01 -1.6704E-02 -4.7142E-01 -6.6721E-03 1.9846E-01 5.8680E-01
1.3992E-02 -4.1149E-02 5.0771E-02

GRADIENT: -1.3365E+01 -1.0384E+01 3.7198E+00 -3.0159E+00 -1.2435E+01 -1.3949E-01
1.1330E+00 -1.2238E+00 -6.1357E+00

0ITERATION NO.: 11 OBJECTIVE VALUE: 464.110749482539 NO. OF FUNC. EVALS.: 10

CUMULATIVE NO. OF FUNC. EVALS.: 124

NPARAMETR: -3.1397E+00 -3.6804E+00 3.4501E+00 2.4636E+00 2.0862E+00 1.7296E+01
4.1557E-01 4.7684E-01 1.1464E+00

PARAMETER: 1.6267E-01 -2.6827E-02 -5.4259E-01 8.3725E-03 2.0862E-01 6.4787E-01
7.5224E-03 7.6282E-02 5.6748E-02

GRADIENT: -9.8717E+00 -4.1703E+00 -2.0344E+00 -3.9657E+00 -2.2063E+01 3.3493E-01 -
7.6780E-01 -1.2049E-01 -1.0300E+00

0ITERATION NO.: 12 OBJECTIVE VALUE: 463.955957595791 NO. OF FUNC. EVALS.: 10

CUMULATIVE NO. OF FUNC. EVALS.: 134

NPARAMETR: -3.1290E+00 -3.6947E+00 3.3137E+00 2.5113E+00 2.2206E+00 1.9383E+01
4.1809E-01 5.9067E-01 1.1565E+00

PARAMETER: 1.6827E-01 -3.4001E-02 -5.8293E-01 2.7563E-02 2.2206E-01 7.6180E-01
1.0546E-02 1.8333E-01 6.1113E-02

GRADIENT: 4.0523E+00 4.8114E+00 -2.4047E+00 -1.6126E-01 -1.3814E+01 2.8635E-01 -
4.1257E-01 2.9871E-01 2.8371E+00

0ITERATION NO.: 13 OBJECTIVE VALUE: 463.893855294881 NO. OF FUNC. EVALS.: 10

CUMULATIVE NO. OF FUNC. EVALS.: 144

NPARAMETR: -3.1288E+00 -3.6965E+00 3.3128E+00 2.5051E+00 2.3083E+00 2.0808E+01
4.2116E-01 6.3780E-01 1.1480E+00

PARAMETER: 1.6836E-01 -3.4931E-02 -5.8319E-01 2.5073E-02 2.3083E-01 8.3273E-01
1.4205E-02 2.2171E-01 5.7438E-02

GRADIENT: 5.4619E-01 -1.0137E-01 -3.6981E-01 7.6447E-01 -2.1651E+00 -1.6371E-02
4.2001E-02 -4.7365E-02 -4.7056E-01

0ITERATION NO.: 14 OBJECTIVE VALUE: 463.885580097708 NO. OF FUNC. EVALS.: 10

CUMULATIVE NO. OF FUNC. EVALS.: 154

NPARAMETR: -3.1287E+00 -3.6962E+00 3.3226E+00 2.4930E+00 2.3416E+00 2.1567E+01
4.2167E-01 6.6089E-01 1.1485E+00

PARAMETER: 1.6841E-01 -3.4742E-02 -5.8023E-01 2.0233E-02 2.3416E-01 8.6859E-01
1.4807E-02 2.3949E-01 5.7668E-02

GRADIENT: -3.1691E-01 -2.7626E-01 -4.9951E-02 1.7020E-01 -3.5189E-01 -1.4713E-02
2.6076E-02 9.8673E-03 -4.3640E-02

0ITERATION NO.: 15 OBJECTIVE VALUE: 463.885036649192 NO. OF FUNC. EVALS.: 10

CUMULATIVE NO. OF FUNC. EVALS.: 164

NPARAMETR: -3.1274E+00 -3.6973E+00 3.3266E+00 2.4879E+00 2.3487E+00 2.1793E+01
4.2183E-01 6.6454E-01 1.1486E+00

PARAMETER: 1.6913E-01 -3.5336E-02 -5.7905E-01 1.8171E-02 2.3487E-01 8.7901E-01
1.4992E-02 2.4224E-01 5.7717E-02

GRADIENT: -9.5874E-02 -8.0028E-02 -1.4626E-03 1.4352E-02 6.8980E-02 -2.4093E-03 -
1.4749E-03 -4.8474E-03 6.4827E-04

0ITERATION NO.: 16 OBJECTIVE VALUE: 463.885020024730 NO. OF FUNC. EVALS.: 10

CUMULATIVE NO. OF FUNC. EVALS.: 174

NPARAMETR: -3.1270E+00 -3.6976E+00 3.3283E+00 2.4867E+00 2.3479E+00 2.1798E+01
4.2190E-01 6.6421E-01 1.1486E+00

PARAMETER: 1.6932E-01 -3.5453E-02 -5.7852E-01 1.7724E-02 2.3479E-01 8.7922E-01
1.5076E-02 2.4200E-01 5.7721E-02

GRADIENT: 6.8426E-02 4.5519E-02 9.9299E-03 7.5181E-04 -6.8060E-03 2.4223E-04 2.6926E-
03 4.5164E-03 8.8324E-03

0ITERATION NO.: 17 OBJECTIVE VALUE: 463.885016299838 NO. OF FUNC. EVALS.: 12

CUMULATIVE NO. OF FUNC. EVALS.: 186

NPARAMETR: -3.1270E+00 -3.6976E+00 3.3283E+00 2.4868E+00 2.3479E+00 2.1798E+01
4.2190E-01 6.6421E-01 1.1486E+00

PARAMETER: 1.6932E-01 -3.5452E-02 -5.7853E-01 1.7728E-02 2.3479E-01 8.7922E-01
1.5075E-02 2.4200E-01 5.7721E-02

GRADIENT: 6.6844E-02 4.4343E-02 9.6906E-03 6.5770E-04 -6.5020E-03 2.2712E-04 2.6261E-
03 4.4030E-03 8.6244E-03

0ITERATION NO.: 18 OBJECTIVE VALUE: 463.885016299838 NO. OF FUNC. EVALS.: 22

CUMULATIVE NO. OF FUNC. EVALS.: 208

NPARAMETR: -3.1270E+00 -3.6976E+00 3.3283E+00 2.4868E+00 2.3479E+00 2.1798E+01
4.2190E-01 6.6421E-01 1.1486E+00

PARAMETER: 1.6932E-01 -3.5452E-02 -5.7853E-01 1.7728E-02 2.3479E-01 8.7922E-01
1.5075E-02 2.4200E-01 5.7721E-02

GRADIENT: -3.5022E-02 -1.4382E-02 -3.1877E-04 -2.9607E-04 -7.0342E-02 -3.5644E-04
2.6261E-03 4.4030E-03 6.6534E-03

0ITERATION NO.: 19 OBJECTIVE VALUE: 463.885016299838 NO. OF FUNC. EVALS.: 24

CUMULATIVE NO. OF FUNC. EVALS.: 232

NPARAMETR: -3.1270E+00 -3.6976E+00 3.3283E+00 2.4868E+00 2.3479E+00 2.1798E+01
4.2190E-01 6.6421E-01 1.1486E+00

PARAMETER: 1.6932E-01 -3.5452E-02 -5.7853E-01 1.7728E-02 2.3479E-01 8.7922E-01
1.5075E-02 2.4200E-01 5.7721E-02

GRADIENT: -3.4749E-02 -1.5007E-02 1.3111E-04 5.1857E-03 -6.9026E-02 -2.4277E-04
1.1381E-03 4.9809E-03 6.1536E-03

#TERM:

0MINIMIZATION 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: 232

NO. OF SIG. DIGITS IN FINAL EST.: 3.9

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: 0.0000E+00 -6.7154E-03 0.0000E+00 0.0000E+00 0.0000E+00 -3.2406E-02

SE: 0.0000E+00 7.7035E-02 0.0000E+00 0.0000E+00 0.0000E+00 4.4467E-02

N: 53 53 53 53 53 53

P VAL.: 1.0000E+00 9.3053E-01 1.0000E+00 1.0000E+00 1.0000E+00 4.6614E-01

ETAshrink(%): 1.0000E+02 1.2832E+01 1.0000E+02 1.0000E+02 1.0000E+02 5.9899E+01

EBVshrink(%): 0.0000E+00 9.7867E+00 0.0000E+00 0.0000E+00 0.0000E+00 6.1200E+01

EPSshrink(%): 8.0350E+00

#TERE:

Elapsed estimation time in seconds: 125.57

Elapsed covariance time in seconds: 201.93

1

****

********** **********

********** FIRST ORDER CONDITIONAL ESTIMATION
****

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

********** **********

****

#OBJV:********** 463.885
****

1

****
*****

******************** ********************

******************** FIRST ORDER CONDITIONAL ESTIMATION
****

******************** FINAL PARAMETER ESTIMATE
****

******************** ********************

****
*****

THETA - VECTOR OF FIXED EFFECTS PARAMETERS *********

TH 1	TH 2	TH 3	TH 4	TH 5	TH 6	TH 7	TH 8
-3.13E+00	-3.70E+00	3.33E+00	2.49E+00	1.77E+00	4.00E+00	2.35E+00	2.18E+01

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS ********

ETA1 ETA2 ETA3 ETA4 ETA5 ETA6

ETA1

+ 0.00E+00

ETA2

+ 0.00E+00 4.22E-01

ETA3

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

ETA4

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

ETA5

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

ETA6

+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 6.64E-01

SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS ****

EPS1

EPS1

+ 1.15E+00

1

OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS *******

	ETA1	ETA2	ETA3	ETA4	ETA5	ETA6
ETA1						
+	0.00E+00					
ETA2						
+	0.00E+00	6.50E-01				
ETA3						
+	0.00E+00	0.00E+00	0.00E+00			
ETA4						
+	0.00E+00	0.00E+00	0.00E+00	0.00E+00		
ETA5						
+	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	
ETA6						
+	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	8.15E-01

SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS ***

	EPS1
EPS1	
+	1.07E+00

1

****
*****

********** **********

********** FIRST ORDER CONDITIONAL ESTIMATION
****

********** STANDARD ERROR OF ESTIMATE
****

********** **********

****
*****

THETA - VECTOR OF FIXED EFFECTS PARAMETERS *********

TH 1	TH 2	TH 3	TH 4	TH 5	TH 6	TH 7	TH 8
2.35E-01	2.72E-01	7.19E-01	6.35E-01	.....	.....	5.63E-01	1.45E+01

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS ********

	ETA1	ETA2	ETA3	ETA4	ETA5	ETA6
ETA1						
+	.....					

ETA2

+ 1.17E-01

ETA3

+ ....

ETA4

+ ....

ETA5

+ ....

ETA6

+ 4.63E-01

SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS ****

EPS1

EPS1

+ 9.63E-02

1

OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS *******

	ETA1	ETA2	ETA3	ETA4	ETA5	ETA6
ETA1						
+	.....					
ETA2						
+	.....	8.97E-02				
ETA3						
+	.....	.....	.....			
ETA4						
+	.....	.....	.....	.....		
ETA5						
+	.....	.....	.....	.....	.....	
ETA6						
+	.....	.....	.....	.....	.....	2.84E-01

SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS ***

	EPS1
EPS1	
+	4.49E-02

1

****
*****

******************** ********************

******************** FIRST ORDER CONDITIONAL ESTIMATION
****

******************** COVARIANCE MATRIX OF ESTIMATE
****

******************** ********************

****
*****

TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7 TH 8 OM11 OM12
OM13 OM14

OM15 OM16 OM22 OM23 OM24 OM25 OM26 OM33 OM34
OM35 OM36 OM44

OM45 OM46 OM55 OM56 OM66 SG11

TH 1

+ 5.54E-02

TH 2

+ -6.15E-02 7.40E-02

TH 3

+ 1.20E-02 3.07E-02 5.17E-01

TH 4

+ -1.30E-01 1.30E-01 -1.89E-01 4.03E-01

TH 5

+ ....

TH 6

+ ....

TH 7

+ -1.06E-02 2.64E-03 -1.38E-01 1.39E-02 .... 3.17E-01

TH 8

+ -4.15E-01 4.94E-01 1.65E+00 -4.67E-01 .... 5.48E+00 2.12E+02

OM11

+ ....

OM12

+ ....

OM13

+ ....

OM14

+ ....

OM15

+ ....

.....

OM16

+ ....

....

OM22

+ 1.36E-02 -1.69E-02 1.65E-02 -3.57E-02 .... -1.04E-02 1.02E-01 ....

.... 1.36E-02

OM23

+ ....

....

OM24

+ ....

....

OM25

+ ....

....

OM26

+ ....

....

1

TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7 TH 8 OM11 OM12 OM13 OM14

OM15 OM16 OM22 OM23 OM24 OM25 OM26 OM33 OM34 OM35 OM36 OM44

OM45 OM46 OM55 OM56 OM66 SG11

OM33

+ ....

....

OM34

+ ....

....

OM35

+ ....

....

OM36

+ ....

....

OM44

+ ....

....

OM45

+ ....

....

.....

OM46

+ ....

....

....

OM55

+ ....

....

....

OM56

+ ....

....

....

OM66

+ 6.19E-03 -1.93E-02 -1.58E-01 -6.46E-03 .... 2.10E-01 2.83E+00 ....

.... -5.30E-03 ....

.... 2.15E-01

SG11

+ -1.85E-04 1.84E-03 -1.51E-03 1.89E-03 .... -6.58E-03 -3.24E-01 ....

.... -2.58E-03 ....

.... 6.73E-03 9.28E-03

1

****

********** **********

********** FIRST ORDER CONDITIONAL ESTIMATION **********

********** CORRELATION MATRIX OF ESTIMATE **********

********** **********

****
*****

TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7 TH 8 OM11 OM12
OM13 OM14

OM15 OM16 OM22 OM23 OM24 OM25 OM26 OM33 OM34
OM35 OM36 OM44

OM45 OM46 OM55 OM56 OM66 SG11

TH 1

+ 2.35E-01

TH 2

+ -9.61E-01 2.72E-01

TH 3

+ 7.07E-02 1.57E-01 7.19E-01

TH 4

+ -8.69E-01 7.56E-01 -4.14E-01 6.35E-01

TH 5

+ ....

TH 6

+ ....

TH 7

+ -7.97E-02 1.72E-02 -3.40E-01 3.89E-02 .... 5.63E-01

TH 8

+ -1.21E-01 1.25E-01 1.57E-01 -5.06E-02 .... 6.68E-01 1.45E+01

OM11

+ ....

OM12

+ ....

OM13

+ ....

OM14

+ ....

OM15

+ ....

.....

OM16

+ ....

....

OM22

+ 4.94E-01 -5.32E-01 1.96E-01 -4.83E-01 .... -1.58E-01 5.99E-02 ....

.... 1.17E-01

OM23

+ ....

....

OM24

+ ....

....

OM25

+ ....

....

OM26

+ ....

....

1

TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7 TH 8 OM11 OM12 OM13 OM14

OM15 OM16 OM22 OM23 OM24 OM25 OM26 OM33 OM34 OM35 OM36 OM44

OM45 OM46 OM55 OM56 OM66 SG11

OM33

+ ....

....

OM34

+ ....

....

OM35

+ ....

....

OM36

+ ....

....

OM44

+ ....

....

OM45

+ ....

....

.....

OM46

+ ....

....

....

OM55

+ ....

....

....

OM56

+ ....

....

....

OM66

+ 5.67E-02 -1.53E-01 -4.73E-01 -2.20E-02 .... 8.03E-01 4.20E-01 ....

.... -9.82E-02 ....

.... 4.63E-01

SG11

+ -8.16E-03 7.01E-02 -2.18E-02 3.09E-02 .... -1.21E-01 -2.31E-01 ....

.... -2.30E-01 ....

.... 1.51E-01 9.63E-02

1

****

********** FIRST ORDER CONDITIONAL ESTIMATION **********

********** INVERSE COVARIANCE MATRIX OF ESTIMATE **********

****

****

TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7 TH 8 OM11 OM12 OM13 OM14

OM15 OM16 OM22 OM23 OM24 OM25 OM26 OM33 OM34 OM35 OM36 OM44

OM45 OM46 OM55 OM56 OM66 SG11

TH 1

+ 1.70E+03

TH 2

+ 1.47E+03 1.40E+03

TH 3

+ -1.28E+02 -1.45E+02 2.33E+01

TH 4

+ 4.67E+01 -1.40E+01 1.29E+01 2.78E+01

TH 5

+ ....

TH 6

+ ....

TH 7

+ -7.08E+01 -7.52E+01 1.08E+01 4.69E+00 .... 2.26E+01

TH 8

+ 1.63E+00 1.60E+00 -3.16E-01 -1.02E-01 .... -3.85E-01 1.59E-02

OM11

+ ....

OM12

+ ....

OM13

+ ....

OM14

+ ....

OM15

+ ....

.....

OM16

+ ....

....

OM22

+ 3.14E+02 3.22E+02 -3.31E+01 -1.12E+00 .... -4.17E+00 6.36E-02 ....
....

.... 1.93E+02

OM23

+ ....

....

OM24

+ ....

....

OM25

+ ....

....

OM26

+ ....

....

1

TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7 TH 8 OM11 OM12 OM13 OM14

OM15 OM16 OM22 OM23 OM24 OM25 OM26 OM33 OM34 OM35 OM36 OM44

OM45 OM46 OM55 OM56 OM66 SG11

OM33

+ ....

....

OM34

+ ....

....

OM35

+ ....

....

OM36

+ ....

....

OM44

+ ....

....

OM45

+ ....

....

.....

OM46

+ ....

....

....

OM55

+ ....

....

....

OM56

+ ....

....

....

OM66

+ 5.27E+01 4.34E+01 5.07E-01 4.54E+00 .... -1.45E+01 3.15E-02 ....

.... 3.91E+00 ....

.... 2.24E+01

SG11

+ -2.32E+02 -2.09E+02 1.45E+01 -3.68E+00 .... 2.62E+01 -3.91E-02 ....

.... -1.27E+01 ....

.... -3.27E+01 1.85E+02

#CPUT: Total CPU Time in Seconds, 328.101

Berkley Madonna Code Used to Generate the Figure 5 Simulations

```
; DPMFIG5 RG 20140410

METHOD RK4
STARTTIME    = 0
STOPTIME     = 8 ; days
DT           = 0.001
DTOUT        = 0.1

parsel=1
tstart[1]=0.5
tstart[2]=1
tstart[3]=2
tstart[4]=3
is=3
eff=10
PORALDOSE=75 ; mg

;==================================
; VT model
;==================================
T'           = - beta * T * V
I'           = beta * T * V - delta * I
V'           = p * I  - c * V

init T       = T0
init I       = 0
init V       = V0

T0           = 4* 10^8
V0           = 10**0.25
delta        = 2.5*dd
c            = 3.3*cc
betalog      = -3.13
beta         = (10^betalog)/bb
plog         = -3.7
p            = 10^plog*10^-inhib/pp

pp = if parsel=1 then if time>=tstart[is] then eff else 1 else 1
bb = if parsel=2 then if time>=tstart[is] then eff else 1 else 1
cc = if parsel=3 then if time>=tstart[is] then eff else 1 else 1
dd = if parsel=4 then if time>=tstart[is] then eff else 1 else 1


; NA Inhibition model
;==================================
inhib   =  IF TIME>=tstart[is] THEN  PORALDOSE/(PORALDOSE+ED50)*Emax ELSE 0
Emax    = 2.35
ED50    = 21.8

;==================================
; VT model output
;==================================
logV         = log10(V)
dl           = 0.5+time*0  ; detetion limit

; END
```

SUPPLEMENTAL FIGURE

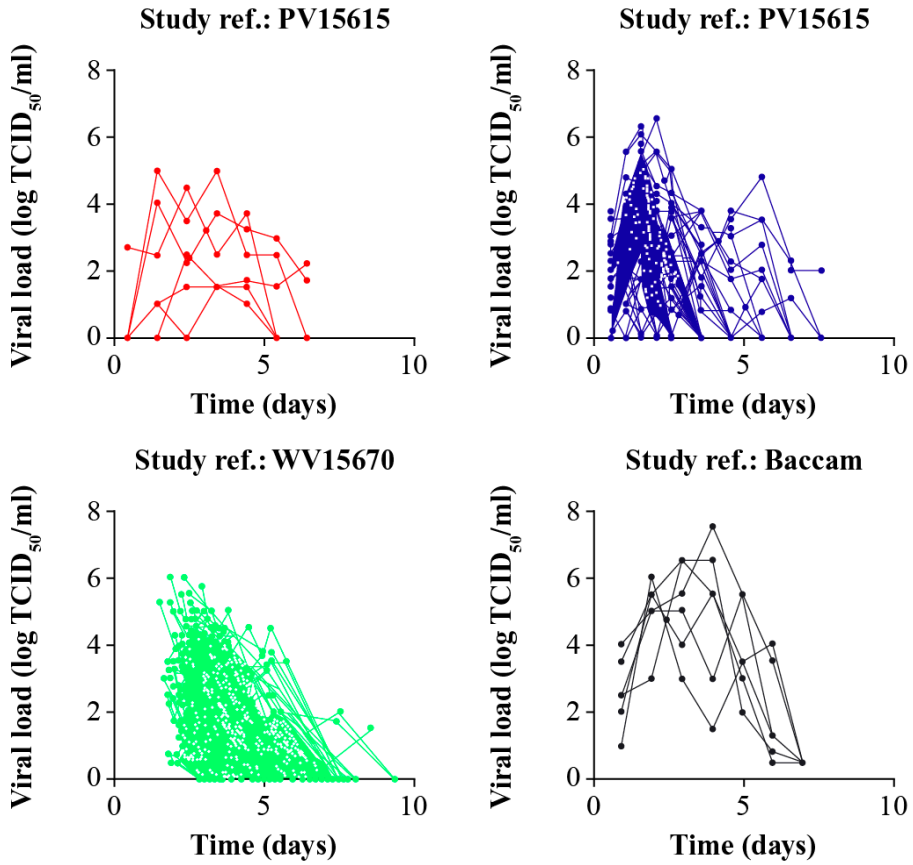

FIG. S1 Individual plots of viral titer versus time for the four clinical studies used to develop the pharmacodynamic model (PV15616, PV15615, WV15670 and Baccam).