

Appendix

NONMEM code for final model

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;;-----;;  
;; Modeller: Fiona Vanobberghen & Melissa Penny & Joel Tarning  
;; Project name: Tribendimidine for Opisthorchis viverrini  
;; Date: 2015-07-16  
;;-----;;  
$PROBLEM    PK Tribendimidine  
;-----  
$INPUT      ID TIME DV AMT CMT MDV EVID BQL STUDY AGE WEIGHT FLUID CRCL  
;-----  
$DATA      data.xls  
           IGNORE=@  
  
;-----  
$SUBROUTINE ADVAN6 TOL=5  
;-----  
$MODEL      COMP=(1)  ; Dose compartment  
           COMP=(2)  ; Metabolite 1 (dADT) central compartment  
           COMP=(3)  ; Metabolite 2 (AdADT) central compartment  
           COMP=(4)  ; Transit compartment 1  
           COMP=(5)  ; Transit compartment 2  
           COMP=(6)  ; Transit compartment 3  
           COMP=(7)  ; Transit compartment 4  
           COMP=(8)  ; Transit compartment 5  
           COMP=(9)  ; Transit compartment 6  
  
;-----  
$PK          ; MTSTUDY-DEFINITION START  
           IF(STUDY.EQ.2) MTSTUDY = 1  ; Most common  
           IF(STUDY.EQ.1) MTSTUDY = ( 1 + THETA(7))  
           ; MTSTUDY-DEFINITION END  
  
           ; MT-RELATION START  
           MTCOV=MTSTUDY  
           ; MT-RELATION END  
  
           ; V2STUDY-DEFINITION START  
           IF(STUDY.EQ.2) V2STUDY = 1  ; Most common  
           IF(STUDY.EQ.1) V2STUDY = ( 1 + THETA(8))  
           ; V2STUDY-DEFINITION END  
  
           ; V2-RELATION START  
           V2COV=V2STUDY  
           ; V2-RELATION END  
  
           ; V3STUDY-DEFINITION START  
           IF(STUDY.EQ.2) V3STUDY = 1  ; Most common  
           IF(STUDY.EQ.1) V3STUDY = ( 1 + THETA(9))  
           ; V3STUDY-DEFINITION END  
  
           ; V3-RELATION START  
           V3COV=V3STUDY  
           ; V3-RELATION END  
  
           ; CMAGE-DEFINITION START  
           CMAGE = ( 1 + THETA(10)*(AGE - 52.00))  
           ; CMAGE-DEFINITION END
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; CM-RELATION START
CMCOV=CMAGE
; CM-RELATION END

; CPAGE-DEFINITION START
CPAGE = ( 1 + THETA(6)*(AGE - 52.00))
; CPAGE-DEFINITION END

; CP-RELATION START
CPCOV=CPAGE
; CP-RELATION END

TVCP = THETA(1)*((WEIGHT/51.50)**0.75)*CPCOV ; Metabolite 1 CL
CP = TVCP*EXP(ETA(1))

TVV2 = THETA(2)*((WEIGHT/51.50)**1.00)*V2COV ; Metabolite 1 V
V2 = TVV2*EXP(ETA(2))

TVCM = THETA(3)*((WEIGHT/51.50)**0.75)*CMCOV ; Metabolite 2 CL
CM = TVCM*EXP(ETA(3))

TVV3 = THETA(4)*((WEIGHT/51.50)**1.00)*V3COV ; Metabolite 2 V
V3 = TVV3*EXP(ETA(4))

TVMT = THETA(5)*MTCOV ; Mean transit time
MT = TVMT*EXP(ETA(5))

S2 = V2 ; Scaling factor CMT2
S3 = V3 ; Scaling factor CMT3

NN = 6
KTR = (NN+1)/MT
K14 = KTR
K45 = KTR
K56 = KTR
K67 = KTR
K78 = KTR
K89 = KTR
K92 = KTR

K20 = CP*0.35/V2 ; Renal elimination
K23 = CP*0.65/V2 ; Hepatic elimination
K30 = CM/V3 ; Hepatic elimination

;-----
$DES DADT (1) = -A(1)*K14
DADT (2) = A(9)*K92 - A(2)*K20 - A(2)*K23
DADT (3) = A(2)*K23 - A(3)*K30
DADT (4) = A(1)*K14 - A(4)*K45
DADT (5) = A(4)*K45 - A(5)*K56
DADT (6) = A(5)*K56 - A(6)*K67
DADT (7) = A(6)*K67 - A(7)*K78
DADT (8) = A(7)*K78 - A(8)*K89
DADT (9) = A(8)*K89 - A(9)*K92
;-----
$ERROR IF(CMT.EQ.2) IPRED = A(2)/S2
IF(CMT.EQ.2) W = SQRT(SIGMA(1,1))

IF(CMT.EQ.3) IPRED = A(3)/S3
IF(CMT.EQ.3) W = SQRT(SIGMA(2,2))

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IF(IPRED.GT.0) IPRED = LOG(IPRED)

; lloq: was 1 ng/ml for plasma, blood and SECOND study DBS
; but was 10 ng/ml for FIRST study DBS
IF(FLUID.EQ.1.OR.FLUID.EQ.2) LLOQ=1
IF(FLUID.EQ.3.AND.STUDY.EQ.2) LLOQ=1
IF(FLUID.EQ.3.AND.STUDY.EQ.1) LLOQ=10

; convert to nanonol/L
IF(CMT.EQ.2) LLOQ = LLOQ*1000/173.214 ; dADT
IF(CMT.EQ.3) LLOQ = LLOQ*1000/215.251 ; adADT

; take logs
LLOQ = LOG(LLOQ)

DUM = (LLOQ-IPRED)/W
CUMD = PHI(DUM)

; Prediction DV>=LOQ
IRES = IPRED-DV
IWRES = IRES/W

IF(BQL.EQ.0.AND.CMT.EQ.2) THEN
F_FLAG = 0
Y = IPRED+ERR(1)
ENDIF

IF(BQL.EQ.0.AND.CMT.EQ.3) THEN
F_FLAG = 0
Y = IPRED+ERR(2)
ENDIF

; Likelihood DV<LOQ
IF(BQL.EQ.1) THEN
F_FLAG = 1
Y = CUMD + 0.000001
ENDIF

;-----
$THETA (0,16.8) ; 1.TVCL_MET1
(0,112) ; 2.TVV2_MET1
(0,42.4) ; 3.TVCL_MET2
(0,30.4) ; 4.TVV3_MET2
(0,2.16) ; 5.MTT
(-0.066,-0.00987,0.071) ; 6.CPAGE1
(-1,1.05,5) ; 7.MTSTUDY1
(-1,0.764,5) ; 8.V2STUDY1
(-1,0.743,5) ; 9.V3STUDY1
(-0.066,-0.0205,0.071) ; 10.CMAGE1
;-----
$OMEGA BLOCK(4) ; full var-cov matrix for CL and V
0.0613
0.171 0.662
-0.129 -0.355 0.847
0.0388 0.497 0.435 1.48
$OMEGA 0.486 ; MTT
;-----
$SIGMA 0.621 ; RUV dADT
0.205 ; RUV adADT

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;-----  
$ESTIMATION  MAXEVAL=9999 POSTHOC METHOD=1 LAPLACIAN INTER  
;-----  
$COVARIANCE  PRINT=E  
;-----
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