NONMEM code for final rifampin population PK model

```
$INPUT
        ID          ; Patient ID
        TIME        ; Time of sample/dose
        DV          ; Dependent variable (natural logarithm of observed concentrations, µg/L)
        WT          ; Body weight (kg, covariate)
        SEX         ; Age (months, covariate)
        DOSE        ; Dose (mg, covariate)
        CSFP        ; CSF protein (g/L, covariate)
        EVID        ; Event ID record
        MDV         ; Missing dependent variable (1=missing)
        AMT         ; Dose amount (mg)
        CMT         ; Compartment

$DATA
        dataset.csv  IGNORE=#

$SUBROUTINE
        ADVAN6 TOL=9

$MODEL
        COMP = (1)          ; Dose compartment
        COMP = (2)          ; Central compartment
        COMP = (3)          ; CSF compartment
        COMP = (4)          ; Enzyme compartment
        COMP = (5)          ; Transit compartment 1
        COMP = (6)          ; Transit compartment 2
        COMP = (7)          ; Transit compartment 3
        COMP = (8)          ; Transit compartment 4
        COMP = (9)          ; Transit compartment 5
```

```
$PK
;------------------------------------ Dose covariate -----------------------------------------------------------------------
        FEMAX = THETA(11)                                    ; Maximum dose effect on relative bioavailability
        FD50 = THETA(12)                                     ; Dose to reach 50% of maximum effect
        CDOSE = 1 + FEMAX * (DOSE-450)/(FD50+(DOSE-450))     ; Dose covariate relationship
;------------------------------------------------------------------------------------------------------------------------------

;------------------------------------ CSF protein covariate-----------------------------------------------------------------
        CCSFP = 1 + (CSFP - 1.6) * THETA(13)                 ; Linear covariate relationship for CSF protein
;------------------------------------------------------------------------------------------------------------------------------

;------------------------------------ Lean bodyweight-----------------------------------------------------------------------
        BMI = WT/(HT**2)                                     ; Calculation of BMI
        IF (SEX.EQ.1) THEN
          LBW = (9270*WT)/(6680+216*BMI)                     ; Lean bodyweight for males
        ENDIF
        IF (SEX.EQ.2) THEN
          LBW = (9270*WT)/(8780+244*BMI)                     ; Lean bodyweight for females
        ENDIF
;------------------------------------------------------------------------------------------------------------------------------
        TVCL = THETA(1) * ((LBW/70)**0.75)                   ; Population clearance
        CL = TVCL * EXP(ETA(1))                              ; Individual clearance

        TVV2 = THETA(2) * (LBW/70)                           ; Population central volume
        V2 = TVV2 * EXP(ETA(2))                              ; Individual central volume

        TVMT = THETA(3)                                      ; Population mean transit time
        MT = TVMT * EXP(ETA(3))                              ; Individual mean transit time

        TVF1 = THETA(4) * CDOSE                              ; Population relative bioavailability
        F1 = TVF1 * EXP(ETA(4))                              ; Individual relative bioavailability
```

```
TVEMAX  = THETA(5)                      ; Maximum increase in enzyme formation rate
EMAX = TVEMAX * EXP(ETA(5))             ; Individual Emax

TVEC50  = THETA(6)                      ; Plasma concentration to reach 50% of Emax
EC50  = TVEC50  * EXP(ETA(6))           ; Individual EC50

TVKENZ  = THETA(7)                      ; Population enzyme degradation rate
KENZ  = TVKENZ * EXP(ETA(7))            ; Individual enzyme degradation rate

TVQ = THETA(8)                          ; Population inter-compartment clearance
Q = TVQ * EXP(ETA(8))                   ; Individual inter-compartment clearance

TVPC  = THETA(9)*CCSFP                  ; Population partition coefficient
PC = TVPC * EXP(ETA(9))                 ; Individual partition coefficient

TVV3 = THETA(10) * (LBW/70)             ; Population CSF volume
V3 = TVV3 * EXP(ETA(10))                ; Individual CSF volume

NN= 5                                   ; Number of transit compartments
KTR = (NN + 1) / MT                     ; Transit rate constant
K15 = KTR                               ; Transit rate constant (COMP 1 --> 5)
K56 = KTR                               ; Transit rate constant (COMP 5 --> 6)
K67 = KTR                               ; Transit rate constant (COMP 6 --> 7)
K78 = KTR                               ; Transit rate constant (COMP 7 --> 8)
K89 = KTR                               ; Transit rate constant (COMP 8 --> 9)
K92 = KTR                               ; Transit rate constant (COMP 9 --> 2)
K20 = CL/V2                             ; Elimination rate constant (COMP 2 --> 0)
K23 = Q * PC/V2                         ; Distribution rate constant (COMP 2 --> 3)
K32 = Q/V3                              ; Distribution rate constant (COMP 3 --> 2)
S2 = V2/1000                            ; Scaling for central volume
S3 = V3/1000                            ; Scaling for CSF volume
```

```
$DES
    CP = A(2)/V2                                    ; Predicted plasma concentration
    EFF = (EMAX * CP) / (EC50 + CP)                 ; Effect of plasma concentration
    DADT (1) = -A(1) * K15                          ; 1 Dose compartment
    DADT (2) = A(9) * K92 - A(2) * A(4) * K20 - A(2)*K23 + A(3)*K32    ; 2 Central compartment
    DADT (3) = A(2)*K23 - A(3)*K32                  ; 3 CSF compartment
    DADT (4) = KENZ * (1 + EFF) - KENZ * A(4)       ; 4 Enzyme compartment
    DADT (5) = A(1) * K15 - A(5) * K56              ; 5 Transit compartment 1
    DADT (6) = A(5) * K56 - A(6) * K67              ; 6 Transit compartment 2
    DADT (7) = A(6) * K67 - A(7) * K78              ; 7 Transit compartment 3
    DADT (8) = A(7) * K78 - A(8) * K89              ; 8 Transit compartment 4
    DADT (9) = A(8) * K89 - A(9) * K92              ; 9 Transit compartment 5

$ERROR
    IF(F.GT.0)  IPRED = LOG(F)                      ; Natural logarithm of predictions
    IF (CMT.EQ.2)    W = SQRT(SIGMA(1,1))           ; Plasma concentration residual error
    IF (CMT.EQ.3)    W = SQRT(SIGMA(2,2))           ; CSF concentration residual error
    IRES = IPRED – DV                               ; Individual residual error
    IWRES = IRES / W                                ; Individual weighted residual error
    IF (CMT.EQ.2)   Y = IPRED + EPS(1)              ; Plasma concentration additive residual error
    IF (CMT.EQ.3)   Y = IPRED + EPS(2)              ; CSF concentration additive residual error

$THETA                                              ; Initial estimates of theta
    (0, 10.1)                                       ; 1. Clearance
    (0, 76)                                         ; 2. Central volume of distribution
    (0, 0.99)                                       ; 3. Mean transit time
    (1) FIX                                         ; 4. Relative bioavailability
    (1.16) FIX                                      ; 5. Maximum increase in enzyme formation rate
    (0.0699) FIX                                    ; 6. Plasma concentration to reach 50% of Emax
    (0.00603) FIX                                   ; 7. Enzyme degradation rate
    (0, 0.00387)                                    ; 8. Inter-compartment clearance
    (0, 0.0712)                                     ; 9. Partition coefficient
    (0.15) FIX                                      ; 10. CSF volume of distribution
```

```
      (0.504) FIX                   ; 11. Maximum effect on relative bioavailability
      (67) FIX                      ; 12. Dose to reach 50% of maximum effect
      (0, 0.141)                    ; 13. CSF protein effect on PC

$OMEGA                              ; Initial estimates for omega
      0.115                         ; 1. Clearance
      0.0462                        ; 2. Central volume of distribution
      0.474                         ; 3. Mean transit time
      0.11                          ; 4. Relative bioavailability
      0 FIX                         ; 5. Maximum increase in enzyme formation rate
      0 FIX                         ; 6. Plasma concentration to reach 50% of Emax
      0 FIX                         ; 7. Enzyme degradation rate
      0.924                         ; 8. Inter-compartment clearance
      0 FIX                         ; 9. Partition coefficient
      0 FIX                         ; 10 CSF volume of distribution

$SIGMA                              ; Initial estimates of sigma
      (0.253)                       ; 1. Plasma concentration residual variability
      (0.49)                        ; 2. CSF concentration residual variability

$ESTIMATION   POSTHOC MAXEVAL=9999   METHOD=1 INTER
```

NONMEM code for final isoniazid population PK model

```
$INPUT
        ID              ; Patient ID
        TIME            ; Time of sample/dose
        DV              ; Dependent variable (natural logarithm of observed concentrations, μg/L)
        WT              ; Body weight (kg, covariate)
        SEX             ; Age (months, covariate)
        EVID            ; Event ID record
        MDV             ; Missing dependent variable (1=missing)
        AMT             ; Dose amount (mg)
        CMT             ; Compartment

$DATA
        dataset.csv  IGNORE=#

$ABBREVIATED COMRES=4

$SUBROUTINE
        ADVAN6 TOL=9

$MODEL
        COMP = (1)              ; Dose compartment
        COMP = (2)              ; Central compartment
        COMP = (3)              ; CSF 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)              ; Plasma AUC compartment
        COMP = (10)             ; CSF AUC compartment
```

```
$MIX
      NSPOP = 2                  ; Number of sub-population
      PMIX   = THETA(9)          ; Probability
      P(2)  = PMIX               ; Probability of subpopulation 2
      P(1)  = 1-PMIX             ; Probability of subpopulation 1
$PK
;----------------------------------- Lean bodyweight---------------------------------------------------------------------------
      BMI = WT/(HT**2)                          ; Calculation of BMI
      IF (SEX.EQ.1) THEN
        LBW = (9270*WT)/(6680+216*BMI)          ; Lean bodyweight for males
      ENDIF
      IF (SEX.EQ.2) THEN
        LBW = (9270*WT)/(8780+244*BMI)          ; Lean bodyweight for females
      ENDIF
;------------------------------------------------------------------------------------------------------------------------------- -------------
      IF (MIXNUM.EQ.1)  THEN
        TVCL = THETA (1) * (LBW/70) ** 0.75     ; Clearance for subpopulation 1
      ENDIF
      IF (MIXNUM.EQ.2)  THEN
       TVCL = THETA (2) * (LBW/70) ** 0.75      ; Clearance for subpopulation 2
      ENDIF
      CL = TVCL * EXP(ETA(1))                   ; Individual clearance

      TVV2 = THETA(3) * (LBW/70)                ; Population central volume
      V2 = TVV2 * EXP(ETA(2))                   ; Individual central volume

      TVMT = THETA(4)                           ; Population mean transit time
      MT = TVMT * EXP(ETA(3))                   ; Individual mean transit time

      TVF1 = THETA(5)                           ; Population relative bioavailability
      F1 = TVF1 * EXP(ETA(4))                   ; Individual relative bioavailability
```

```
    TVQ = THETA(6)                          ; Population inter-compartment clearance
    Q = TVQ * EXP(ETA(5))                   ; Individual inter-compartment clearance

    TVPC  = THETA(7)                        ; Population partition coefficient
    PC = TVPC * EXP(ETA(6))                 ; Individual partition coefficient

    TVV3 = THETA(8) * (LBW/70)              ; Population CSF volume
    V3 = TVV3 * EXP(ETA(7))                 ; Individual CSF volume

    NN= 5                                   ; Number of transit compartments
    KTR = (NN + 1) / MT                     ; Transit rate constant
    K14 = KTR                               ; Transit rate constant (COMP 1 --> 4)
    K45 = KTR                               ; Transit rate constant (COMP 4 --> 5)
    K56 = KTR                               ; Transit rate constant (COMP 5 --> 6)
    K67 = KTR                               ; Transit rate constant (COMP 6 --> 7)
    K78 = KTR                               ; Transit rate constant (COMP 7 --> 8)
    K82 = KTR                               ; Transit rate constant (COMP 8 --> 2)
    K20 = CL/V2                             ; Elimination rate constant (COMP 2 --> 0)
    K23 = Q * PC/V2                         ; Distribution rate constant (COMP 2 --> 3)
    K32 = Q/V3                              ; Distribution rate constant (COMP 3 --> 2)
    S2 = V2/1000                            ; Scaling for central volume
    S3 = V3/1000                            ; Scaling for CSF volume

    IF(NEWIND.LE.1) THEN                    ; Assign negative value for the new subject
       COM(1)=-1                            ; Holder of plasma Cmax
       COM(2)=-1                            ; Holder of plasma Tmax
       COM(3)=-1                            ; Holder of CSF Cmax
       COM(4)=-1                            ; Holder of CSF Tmax
    ENDIF

$DES
    DADT (1) = -A(1) * K14                  ; 1 Dose compartment
    DADT (2) = A(8) * K82 - A(2) * K20 - A(2)*K23 + A(3)*K32  ; 2 Central compartment
```

```
    DADT (3) = A(2)*K23 - A(3)*K32                ; 3 CSF compartment
    DADT (4) = A(1) * K14 - A(4) * K45            ; 4 Transit compartment 1
    DADT (5) = A(4) * K45 - A(5) * K56            ; 5 Transit compartment 2
    DADT (6) = A(5) * K56 - A(6) * K67            ; 6 Transit compartment 3
    DADT (7) = A(6) * K67 - A(7) * K78            ; 7 Transit compartment 4
    DADT (8) = A(7) * K78 - A(8) * K82            ; 8 Transit compartment 8

    DADT (9) = A(2)                               ; 9 Accumulated plasma amount
    AUC_P = A(9)/S2                               ; Plasma AUC
    DADT (10) = A(3)                              ; 10 Accumulated CSF amount
    AUC_C = A(10)/S3                              ; CSF AUC

    CT=A(2)/S2                                    ; Plasma concentration
    IF(CT.GT.COM(1)) THEN
      COM(1)=CT                                   ; Plasma Cmax
      COM(2)=T                                    ; Plasma Tmax
    ENDIF

    CCSF=A(3)/S3                                  ; CSF concentration
    IF(CCSF.GT.COM(3)) THEN
      COM(3)=CCSF                                 ; CSF Cmax
      COM(4)=T                                    ; CSF Tmax
    ENDIF

$ERROR
    IF(F.GT.0)  IPRED = LOG(F)                    ; Natural logarithm of predictions
    IF (CMT.EQ.2)    W = SQRT(SIGMA(1,1))         ; Plasma concentration residual error
    IF (CMT.EQ.3)    W = SQRT(SIGMA(2,2))         ; CSF concentration residual error
    IRES = IPRED – DV                             ; Individual residual error
    IWRES = IRES / W                              ; Individual weighted residual error
    IF (CMT.EQ.2)   Y = IPRED + EPS(1)            ; Plasma concentration additive residual error
    IF (CMT.EQ.3)   Y = IPRED + EPS(2)            ; CSF concentration additive residual error
```

```
	CMAX_P  = COM(1)			; Output plasma Cmax
	TMAX_P  = COM(2)			; Output plasma Tmax
	CMAX_C  = COM(3)			; Output CSF Cmax
	TMAX_C  = COM(4)			; Output CSF Tmax

$THETA					; Initial estimates of theta
	(0, 40.7)				; 1. Clearance for subpopulation 1
	(0, 18.1)				; 2. Clearance for subpopulation 2
	(0, 96.7)				; 3. Central volume of distribution
	(0, 0.357)				; 4. Mean transit time
	(1) FIX					; 5. Relative bioavailability
	(0, 0.0344)				; 6. Inter-compartment clearance
	(1) FIX					; 7. Partition coefficient
	(0.15) FIX				; 8. CSF volume of distribution
	(0, 0.399)				; 9. Probability of subpopulation 2

$OMEGA					; Initial estimates for omega
	0.0215					; 1. Clearance
	0 FIX					; 2. Central volume of distribution
	1.05					; 3. Mean transit time
	0.212					; 4. Relative bioavailability
	0.516					; 5. Inter-compartment clearance
	0 FIX					; 6. Partition coefficient
	0 FIX					; 7. CSF volume of distribution

$SIGMA					; Initial estimates of sigma
	(0.299)					; 1. Plasma concentration residual variability
	(0.274)					; 2. CSF concentration residual variability

$ESTIMATION   POSTHOC MAXEVAL=9999   METHOD=1 INTER
```

NONMEM code for final isoniazid population PD model

```
$INPUT
        ID              ; Patient ID
        TIME            ; Time of sample/dose
        DV              ; Dependent variable (1 = Death, 0 = survival)
        CMT             ; Compartment
        EVID            ; Event ID record
        HIV             ; Covariate (1 = HIV co-infection, 0 = no HIV co-infection)
        GCS             ; Covariate (Glasgow coma score)
        CMAXC           ; Isoniazid CSF maximum concentration (µg/L)

$DATA
        dataset.csv  IGNORE=#

$SUBROUTINE
        ADVAN6 TOL=3

$MODEL
        COMP = (1)              ; Hazard

$PK
;------------------------------------ Isoniazid CSF Cmax effect---------------------------------------------------------------------
        EMAX = THETA(5)                         ; Maximum effect on hazard
        EC50 = THETA(6)                         ; CSF Cmax to reach 50% of maximum effect
        HILL = THETA(7)                         ; Shape parameter
        EFF = 1 - EMAX*CMAXC**HILL/(CMAXC**HILL+EC50**HILL)
                                                ; CSF Cmax effect
;-------------------------------------------------------------------------------------------------------------------------------------

;------------------------------------ GCS covariate------------------------------------------------------------------------------------
        CGCS =   1 + THETA(3)*(GCS-14)          ; Linear covariate relationship for GCS
;-------------------------------------------------------------------------------------------------------------------------------------
```

```
;------------------------------------ HIV covariate------------------------------------------------------------------------------------
        CHIV =   1 + THETA(4)*HIV                        ; Linear covariate relationship for HIV
;------------------------------------------------------------------------------------------------------------------------------------

        TVSIGCE  = THETA(1)                              ; Standard deviation of log-normal distribution
        SIGCE = TVSIGCE + ETA(1)                         ; Individual standard deviation
        TVMUCE   = THETA(2)  * CGCS * CHIV               ; Median of log-normal distribution
        MUCE = TVMUCE + ETA(2)                           ; Individual median
        PI = 3.1415                                      ; Pi value

$DES
        DEL   = 1E-16                                    ; Small number to avoid LOG(0)
        TIMX   = T+DEL                                   ; Time
        LTIMX  = LOG(TIMX)                               ; Natural Log transformation of time
        X2X    = (LTIMX-MUCE)/SIGCE                      ; Part 1 of log-normal distribution
        PDF2X  = EXP(-(1/2)*(X2X**2))/SQRT(2*PI)         ; Part 2 of log-normal distribution
        LOGCEX = ((1/(TIMX*SIGCE))*PDF2X/(1-PHI(X2X))) *EFF          ; Log-normal distribution
        DADT(1)= LOGCEX                                  ; Log-normal distribution hazard

$ERROR
        DE    = 1E-16                                    ; Small number to avoid LOG(0)
        TIM    = TIME+DE                                 ; Time
        LTIM   = LOG(TIM)                                ; Natural Log transformation of time
        CHZ   = A(1)                                     ; Cumulative hazard
        SUR   = EXP(-CHZ)                                ; Survival function

        X2     = (LTIM-MUCE)/SIGCE                       ; Part 1 of log-normal distribution
        PDF2   = EXP(-(1/2)*(X2**2))/SQRT(2*PI)          ; Part 2 of log-normal distribution
        LOGCE  = ((1/(TIM*SIGCE))*PDF2/(1-PHI(X2)))*EFF  ; Log-normal distribution
        HAZ    = LOGCE                                   ; Log-normal distribution hazard
```

```
    IF(DV.EQ.0) THEN
      PR = SUR                          ; Censored event (probability of survival)
     ENDIF
    IF (DV.EQ.1) THEN
      PR = SUR * HAZ                    ; Observed event
    ENDIF
    Y = PR
$THETA                                  ; Initial estimates of theta
    (0, 1.18)                           ; 1. Standard deviation
    (0, 3.42)                           ; 2. Median
    (0, 0.0907)                         ; 3. GCS effect on median
    (-0.5, -0.276)                      ; 4. HIV effect on median
    (0.99) FIX                          ; 5. Maximum effect of CSF Cmax
    (0, 1.37)                           ; 6. CSF Cmax to reach 50% of maximum effect
    (0, 2.8)                            ; 7. Shape parameter

$OMEGA                                  ; Initial estimates for omega
    0 FIX                               ; 1. Standard deviation
    0 FIX                               ; 2. Median

$ ESTIMATION MAXEVAL=9999 POSTHOC METHOD=1 MCETA=500 LAPLACIAN LIKE NUMERICAL
```