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| [**WorldWide Antimalarial Resistance Network**](https://www.wwarn.org/impact-outcomes/publications/population-pharmacokinetic-properties-piperaquine-falciparum-malaria)  [Pharmacometric Scientific Group](https://www.wwarn.org/working-together/scientific-groups)  Version 1. Created April 2019. |
| WWARN is committed to supporting efficient and quality data collection and analysis for antimalarial drug research. As such we are sharing the NONMEM code used for this publication. NONMEM is a computer program, NONlinear Mixed Effects Modeling, used by WWARN’s [Pharmacometric Scientific Group](https://www.wwarn.org/working-together/scientific-groups).  For further information, please contact [info@wwarn.org](mailto:info@wwarn.org) |
| **Please use the following reference:**  WWARN NONMEM file used to develop: Population Pharmacokinetics of the Antimalarial Amodiaquine: a Pooled Analysis To Optimize Dosing.  Ali AM, Penny MA, Smith TA, Workman L, Sasi P, Adjei GO, Aweeka F, Kiechel JR, Jullien V, Rijken MJ, McGready R, Mwesigwa J, Kristensen K, Stepniewska K, Tarning J, Barnes KI, Denti P; WWARN Amodiaquine PK Study Group.  Antimicrob Agents Chemother. 2018;62(10). pii: e02193-17. |
| $INPUT  ID ; Patient ID  TIME ; Time of sample  DV ; Dependent variable (natural logarithm of observed concentrations, nmol/L)  WT ; Body weight (covariate, kg)  AGE ; Age (covaraite, years)  EVID ; Event ID record  MDV ; Missing dependent variable (1=missing)  AMT ; Dose amount (μmol)  CMT ; Compartment (1=dose, 2=amodiaquine (AQ), 4=desethylamodiaquine (DAQ))  OCC ; Occasion (1=first dose, 2=second dose , 3=third dose)  LOQ ; Limit of quantification  $DATA  dataset.csv IGNORE=#  $SUBROUTINE  ADVAN13 TOL=8 TRANS1  $MODEL  COMP = (1) ; Dose  COMP = (2) ; AQ central compartment  COMP = (3) ; AQ peripheral compartment  COMP = (4) ; DAQ central compartment  COMP = (5) ; DAQ first peripheral compartment  COMP = (6) ; DAQ second peripheral compartment  $PRIOR  NWPRI NPEXP = 1 PLEV = 0.9999 ; Prior information for the maturation function  $THETAP 0.02 FIX ; Log postmenstrual age to reach 50% of full maturation for AQ  $THETAP 1.25 FIX ; Log shape parameter for AQ  $THETAP 0.02 FIX ; Log postmenstrual to reach 50% of full maturation for DAQ  $THETAP 1.25 FIX ; Log shape parameter for DAQ  $THETAPV BLOCK(4) FIX ; THETA BLOCK  0.01  0 0.01  0 0 0.01  0 0 0 0.01  $PK  ;------------------------------------Age covariate for AQ -------------------------------------------------------------------------  PGA = AGE+(9/12) ; Postmenstrual age (years)  MEDAGE = 8.1 ; Median age (years)  TV\_PGA = MEDAGE+(9/12) ; Median postmenstrual age (years)  LOGPGA50 = THETA(1) ; Log postmenstrual age to reach 50% of full maturation for AQ  GAMMA1 = THETA(2) ; Shape parameter for AQ  MATCL = 1/(1+EXP(-GAMMA1\*(LOG(PGA)-LOGPGA50)))\* (1+EXP(-GAMMA1\*(LOG(TV\_PGA)-  LOGPGA50))) ; Postmenstrual age-maturation relationship for AQ  ;----------------------------------------------------------------------------------------------------------------------------------------  ;------------------------------------Age covariate for DAQ ----------------------------------------------------------------------  LOGPGA50\_DAQ = THETA(3) ; Log postmenstrual age to reach 50% of full maturation for DAQ  GAMMA2 = THETA(4) ; Shape parameter for DAQ  MATCLDAQ = 1/(1+EXP(-GAMMA2\*(LOG(PGA)-LOGPGA50\_DAQ)))\*(1+EXP(-GAMMA2\*  (LOG(TV\_PGA)-LOGPGA50\_DAQ))) ; Postmenstrual age-maturation relationship for DAQ  ;----------------------------------------------------------------------------------------------------------------------------------------  ;------------------------------------ First dose covariate --------------------------------------------------------------------------  IF (OCC.GT.1) OCC\_BIO = 1 ; Dose effect  IF (OCC.EQ.1) OCC\_BIO = 1 + THETA(19) ; Proportional effect for first dose  ;----------------------------------------------------------------------------------------------------------------------------------------  ;------------------------------------ Between occasion variability (BOV) -----------------------------------------------------  BOV\_MTT = ETA(11) ; BOV for mean transit time  IF (OCC.EQ.2) BOV\_MTT = ETA(12) ; Occasion 2  IF (OCC.EQ.3) BOV\_MTT = ETA(13) ; Occasion 3  BOV\_KA = ETA(14) ; BOV for absorption rate  IF(OCC.EQ.2) BOV\_KA = ETA(15) ; Occasion 2  IF(OCC.EQ.3) BOV\_KA = ETA(16) ; Occasion 3  BOV\_BIO = ETA(17) ; BOV for relative bioavailability  IF (OCC.EQ.2) BOV\_BIO = ETA(18) ; Occasion 2  IF (OCC.EQ.3) BOV\_BIO = ETA(19) ; Occasion 3  ;----------------------------------------------------------------------------------------------------------------------------------------  TVCL = THETA(5) \* ((WT/49)\*\*0.75) \* MATCL ; Population AQ clearance  CL = TVCL \* EXP(ETA(1)) ; Individual AQ clearance  TVV2 = THETA(6) \* (WT/49) ; Population AQ central volume  V2 = TVV2 \* EXP(ETA(2)) ; Individual AQ central volume  TVQ1 = THETA(7) \* ((WT/49)\*\*0.75) ; Population AQ inter-compartment clearance  Q1 = TVQ1 \* EXP(ETA(3)) ; Individual AQ inter-compartment clearance  TVV3 = THETA(8) \* (WT/49) ; Population AQ peripheral volume  V3 = TVV3 \* EXP(ETA(4)) ; Individual AQ peripheral volume  TVKA = EXP(THETA(9)) ; Population absorption rate constant  KA = TVKA \* EXP(BOV\_KA) ; Individual absorption rate constant  TVMTT = THETA(10) ; Population mean transit time  MTT = TVMTT \* EXP(BOV\_MTT) ; Individual mean transit time  TVNN = EXP(THETA(11)) ; Population number of transit compartments  NN = TVNN ; Individual number of transit compartments  TVBIO = THETA(12) \* OCC\_BIO ; Population relative bioavailability  BIO = TVBIO \* EXP(BOV\_BIO) ; Individual relative bioavailability  TVV4 = THETA(13) \* (WT/49) ; Population DAQ central volume  V4 = TVV4 \* EXP(ETA(5)) ; Individual DAQ central volume  TVCLM = THETA(14)\*((WT/49)\*\*0.75)\*MATCLDAQ ; Population DAQ clearance  CLM = TVCLM \* EXP(ETA(6)) ; Individual DAQ clearance  TVQ2 = THETA(15) \* ((WT/49)\*\*0.75) ; Population DAQ inter-compartment clearance1  Q2 = TVQ2\* EXP(ETA(7)) ; Individual DAQ inter-compartment clearance1  TVV5 = THETA(16) \* (WT/49) ; Population DAQ peripheral volume 1  V5 = TVV5 \* EXP(ETA(8)) ; Individual DAQ peripheral volume 1  TVQ3 = THETA(17) \* ((WT/49)\*\*0.75) ; Population DAQ inter-compartment clearance2  Q3 = TVQ2 \* EXP(ETA(9)) ; Individual DAQ inter-compartment clearance2  TVV6 = THETA(18) \* (WT/49) ; Population DAQ peripheral volume 2  V6 = TVV6 \* EXP(ETA(10)) ; Individual DAQ peripheral volume 2  K23 = Q1/V2 ; AQ distribution rate constant (COMP 2 --> 3)  K32 = Q1/V3 ; AQ distribution rate constant (COMP 3 --> 2)  K24 = CL / V2 ; AQ elimination rate constant (COMP 2 --> 4)  K45 = Q2/V4 ; DAQ distribution rate constant (COMP 4 --> 5)  K54 = Q2/V5 ; DAQ distribution rate constant (COMP 5 --> 4)  K46 = Q3/V4 ; DAQ distribution rate constant (COMP 4 --> 6)  K64 = Q3/V6 ; DAQ distribution rate constant (COMP6 --> 4)  K40 = CLM / V4 ; DAQ elimination rate constant (COMP 4 --> 0)  F1 = 0 ; The extent of absorption for dosing compartment 1  S2 = V2/1000 ; Scaling for AQ central volume  S4 = V4/1000 ; Scaling for DAQ central volume  IF (NEWIND.NE.2.OR.EVID.GE.3) THEN ; Beginning of new individual  TNXD = TIME ; Initial time  PNXD = AMT ; Initial dose  ENDIF  TDOS = TNXD ; Initial time to variable TDOS  PD = PNXD ; Initial dose to variable PD  IF (AMT.GT.0) THEN  TNXD = TIME ; Time of dose  PNXD = AMT ; Dose amount  ENDIF  KTR = (NN+1)/MTT ; Transfer rate constant  PIZZA = LOG(BIO\*PD\*KTR + 0.00001) - GAMLN(NN+1) ; Stirling approximation  $DES  TEMPO = T – TDOS ; Time after dose  INPUT = 0 ; Initialization the dose input  IF (PD.GT.0.AND.TEMPO.GT.0) THEN  INPUT = EXP(PIZZA+NN\*LOG(KTR\*TEMPO)-KTR\*TEMPO) ; Input of dose  ENDIF  DADT(1) = INPUT - KA\*A(1) ; 1 Dose compartment  DADT(2) = KA\*A(1) - K23\*A(2) + K32\*A(3) -K24\*A(2) ; 2 AQ central compartment  DADT(3) = K23\*A(2) - K32\*A(3) ; 3 AQ peripheral compartment  DADT(4) = K24\* A(2) - K45\*A(4) + K54\*A(5)-  K46\*A(4) + K64\*A(6) -K40\*A(4) ; 4 DAQ central compartment  DADT(5) = K45\*A(4) - K54\*A(5) ; 5 DAQ peripheral compartment 1  DADT(6) = K46\*A(4) - K64\*A(6) ; 6 DAQ peripheral compartment 2  $ERROR  IF (CMT = 2) THEN  IPRED = A(2)/S2 ; Predicted plasma concentration of AQ  ADD = THETA(20) + LOQ/5 ; AQ additive residual error  PROP = THETA(21)\*IPRED ; AQ proportional residual error  ENDIF  IF (CMT = 4) THEN  IPRED = A(4)/S4 ; Predicted plasma concentration of DAQ  ADD = THETA(22) + LOQ/5 ; DAQ additive residual error  PROP = THETA(23)\*IPRED ; DAQ proportional residual error  ENDIF  W = SQRT(ADD\*\*2+PROP\*\*2) ; Residual error  IRES = DV-IPRED ; Individual residue  IF (W.LE.0.0001) W = 0.0001  IWRES = IRES/W ; Individual weighted residue  Y = IPRED + W\*EPS(1) ; Prediction of Y  ;----------------------------------------------------------------------------------------------------------------------------------------  $THETA ; Initial estimates of theta  (-1,-0.017,1.5) ; 1. Postmenstrual age to reach 50% of full maturation for AQ (log)  (-1,1.28,2) ; 2. Shape parameter (log)  (-1,0.072,1.5) ; 3 . Postmenstrual age to reach 50% of full maturation for DAQ (log)  (-1,1.17,2) ; 4. Shape parameter (log)  (0,2960,10000) ; 5. AQ clearance  (0,13500,30000) ; 6. AQ central volume of distribution  (10,2310,10000) ; 7. AQ inter-compartment clearance  (0,22700,50000) ; 8. AQ peripheral volume of distribution  (-1,-0.529,2) ; 9. Absoprtion rate constant in log scale  (0.1,0.236,4) ; 10. Mean transit time  (0,0.647,5) ; 11. Number of transit compartments in log scale  (1) FIX ; 12. Relative bioavailability  (10,258,5000) ; 13. DAQ central volume of distribution  (10,32.6,1000) ; 14. DAQ clearance  (5,154,1000) ; 15. DAQ inter-compartment clearance 1  (100,2460,5000) ; 16. DAQ peripheral volume of distribution 1  (10,31.3,1000) ; 17. DAQ inter-compartment clearance 2  (500,5580,10000) ; 18. DAQ peripheral volume of distribution 2  (-1,-0.224,6) ; 19. First dose occasion on bioavailability  (0.1,0.445,10) ; 20. Additive residul error for AQ  (0.1,0.199,0.5) ; 21. Proportional residue for AQ  0 FIX ; 22. Additive residul error for DAQ  (0.1,0.242,0.7) ; 23. Proportional residul error for DAQ  $OMEGA ; Initial estimates for omega  0.104 ; 1. AQ IIV clearance  0.282 ; 2. AQ IIV central volume  0 FIX ; 3. AQ IIV inter-compartment clearance  0 FIX ; 4. AQ IIV peripheral volume  0.452 ; 5. DAQ IIV central volume  0.040 ; 6. DAQ IIV clearance  0 FIX ; 7. DAQ IIV inter-compartment clearance 1  0 FIX ; 8. DAQ IIV peripheral volume 1  0 FIX ; 9. DAQ IIV inter-compartment clearance 2  0 FIX ; 10. DAQ IIV peripheral volume 2  $OMEGA BLOCK(1) 0.872 ; 11. BOV for mean transit time  $OMEGA BLOCK(1) SAME ; 12. Occasion 2  $OMEGA BLOCK(1) SAME ; 13. Occasion 3  $OMEGA BLOCK(1) 0.617 ; 14. BOV for absorption rate constant  $OMEGA BLOCK(1) SAME ; 15. Occasion 2  $OMEGA BLOCK(1) SAME ; 16. Occasion 3  $OMEGA BLOCK(1) 0.096 ; 17. BOV for bioavailability  $OMEGA BLOCK(1) SAME ; 18. Occasion 2  $OMEGA BLOCK(1) SAME ; 19. Occasion 3  $SIGMA ; Initial estimates of sigma  1 FIX ; Residual variability  $ESTIMATION POSTHOC MAXEVAL=9999 METHOD=1 INTER |