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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  |
| **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 |