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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 10 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 **Code 1** file used to develop: [Artemether-lumefantrine dosing for malaria treatment in young children and pregnant women: a pharmacokinetic-pharmacodynamic meta-analysis.](https://www.wwarn.org/impact-outcomes/publications/artemether-lumefantrine-dosing-malaria-treatment-young-children-and)  F. Kloprogge, L. Workman, S. Borrmann, M. Tékété, G. Lefèvre, K. Hamed, P. Piola, J. Ursing, P.E. Kofoed, A. Mårtensson, B. Ngasala, A. Björkman, M. Ashton, S.F. Hietala, F. Aweeka, S. Parikh, L. Mwai, T.M.E. Davis, H. Karunajeewa, S. Salman, F. Checchi, C. Fogg, P.N. Newton, M. Mayxay, P. Deloron, J.F. Faucher, F. Nosten, E.A. Ashley, R. McGready, M. van Vugt, S. Proux, R.N. Price, J. Karbwang, F. Ezzet, R. Bakshi,  K. Stepniewska, N.J. White, P.J. Guerin, K.I. Barnes, J. Tarning.  *PLoS Medicine*. 2018 Jun 12;15(6):e1002579.  Read the full summary of the [Antimalarial – Lumefantrine POP/PK Study Group](https://www.wwarn.org/working-together/study-groups/antimalarial-lumefantrine-poppk-study-group) |
| $INPUT  ID ; Patient ID  TIME ; Time of sample  DV ; Dependent variable (natural logarithm of observed concentrations, nmol/L)  WT ; Body weight (covariate)  EVID ; Event ID record  MDV ; Missing dependent variable (1=missing)  AMT ; Dose amount (μmol)  CMT ; Compartment (1=dose, 2=lumefantrine)  PREG ; Pregnancy (covariate; 0=non-pregnant, 1=pregnant)  LNPC ; Parasite count (covariate; logarithm of parasite count)  DOSE ; Lumefantrine dosage (covariate; mg/kg)  $DATA  dataset.csv IGNORE=#  $SUBROUTINE  ADVAN4 TRANS1  $PK  ;------------------------------------Dose covariate----------------------------------------------------------------------  D50 = THETA(7) ; Dose (mg/kg) to reach 50% of full saturation effect  DS = 1 - (DOSE/(DOSE+D50) ) ; Dose (mg/kg) covariate relationship  ;------------------------------------------------------------------------------------------------------------------------------------  ;------------------------------------ Pregnancy covariate ----------------------------------------------------------------  PREGNANCY = (1 + THETA(8) \* PREG) ; Linear covariate relationship for pregnancy  ;------------------------------------------------------------------------------------------------------------------------------------  ;------------------------------------Parasite biomass covariate-------------------------------------------------------------  PARASITE = ((LNPC /4.20)\*\*THETA(9)) ; Power covariate relationship for parasite biomass  ;------------------------------------------------------------------------------------------------------------------------------------  TVCL = THETA(1) \* ((WT/42)\*\*0.75) ; Population clearance  CL = TVCL \* EXP(ETA(1)) ; Individual clearance  TVV = THETA(2) \* ((WT/42)\*\*1) ; Population central volume  V = TVV \* EXP(ETA(2)) ; Individual central volume  TVQ = THETA(3) \* ((WT/42)\*\*0.75) ; Population inter-compartment clearance  Q = TVQ \* EXP(ETA(3)) ; Individual inter-compartment clearance  TVVP = THETA(4) \* ((WT/42)\*\*1) ; Population peripheral volume  VP = TVVP \* EXP(ETA(4)) ; Individual peripheral volume  TVKA = THETA(5) \* PREGNANCY ; Population absorption rate constant  KA = TVKA \* EXP(ETA(5)) ; Individual absorption rate constant  TVF1 = THETA(6) \* DS \* PARASITE ; Population relative bioavailability  BXPAR = THETA(10) ; Box-Cox shape parameter  PHI = EXP(ETA(6)) ; Exponential of IIV  ETATR = (PHI\*\*BXPAR-1)/BXPAR ; Box-Cox tranfomation of IIV  F1 = TVF1 \* EXP(ETATR) ; Individual relative bioavailability  K = CL/V ; Elimination rate constant (COMP 2 --> 0)  K23 = Q/V ; Distribution rate constant (COMP 2 --> 3)  K32 = Q/VP ; Distribution rate constant (COMP 3 --> 2)  S2 = V /1000 ; Scaling for central volume    $ERROR  IPRED = A(2) / S2 ; Predicted plasma concentration  IF(IPRED.GT.0) IPRED = LOG(IPRED) ; Natural logarithm of predictions  W = SQRT(SIGMA(1,1)) ; Residual error  IRES = IPRED – DV ; Individual residual error  IWRES = IRES / W ; Individual weighted residual error  Y = IPRED + EPS(1) ; Additive residue error  ;------------------------------------------------------------------------------------------------------------------------------------  $THETA ; Initial estimates of theta  (0, 1.35) ; 1. Clearance  (0, 11.2) ; 2. Central volume of distribution  (0, 0.344) ; 3. Inter-compartment clearance  (0, 59.0) ; 4. Peripheral volume of distribution  (0, 0.0386) ; 5. Absoprtion rate constant  (1 FIX) ; 6. Relative bioavailability  (0, 3.86) ; 7. Dose (mg/kg) to reach 50% of full absoption  (-1, 0.352) ; 8. Pregnancy on absoprtion rate constant  (-1, -0.643) ; 9. Parasite biomass on relative bioavailability  (-1, -0.343) ; 10. Box-Cox shape parameter  $OMEGA ; Initial estimates for omega  (0 FIX) ; 1. IIV clearance  (1.12) ; 2. IIV central volume of distribution  (0 FIX) ; 3. IIV Inter-compartment clearance  (0 FIX) ; 4. IIV peripheral volume of distribution  (0 FIX) ; 5. IIV absorption rate constant  (0.402) ; 6. IIV relative bioavailability  $SIGMA ; Initial estimates of sigma  (0.323) ; Residual variability  $ESTIMATION POSTHOC MAXEVAL=9999 METHOD=1 INTER |